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South Russian Journal of Cancer

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The "South Russian Journal of Cancer" is a quarterly scientific and practical peer–reviewed journal. A professional medical publication that reflects the results of current research on the subject of publications: diagnosis and treatment of oncological diseases, issues of carcinogenesis and molecular oncology, new medicines and technologies. It was founded in 2019.

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- High-quality published content that includes the latest and trustworthy scientific papers, research or work on oncology issues.

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- Informing readers about the results of major medical forums;
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Журнал входит в рекомендованный ВАК РФ перечень рецензируемых научных журналов и изданий для опубликования основных научных результатов диссертаций на соискание учёной степени кандидата и доктора наук.

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- Содействие обмену опытом и передаче передовых знаний между специалистами;
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Журнал принимает к публикации: результаты оригинальных исследований, обзоры литературы, описание клинических случаев.

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ORIGINAL ARTICLE

Clinical and pathogenetic justification for the use of therapeutic plasma exchange in the complex of preoperative preparation of patients with non-small cell lung cancer complicated by the inflammatory process

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ABSTRACT

Purpose of the study. Determination of pathogenetic substantiation and indication criteria for the inclusion of extracorporeal detoxification methods in preoperative preparation of patients with non-small cell lung cancer (NSCLC) complicated by inflammation.

Patients and methods. This study included the data on 222 patients with newly diagnosed stage I–IV NSCLC referred for elective surgical treatment to the Department of Thoracic Oncology, National Medical Centre for Oncology, in 2017–2019. Endogenous intoxication was evaluated in all patients depending on the leukogram results: leukocytic intoxication index (LII), body resistance index (BRI), reactive neutrophil response (RNR), and neutrophil-lymphocyte ratio (NLR). Indicators of the inflammatory response, i.e. interleukin 6 and procalcitonin, were also studied.

Results. 36.5 % of NSCLC patients developed inflammation. That over 70 % of the NSCLC patients showed pronounced clinical and laboratory signs of endogenous intoxication and inhibited protective systems of homeostasis. Initial sub- or decompensated endotoxicosis together with reduced overall reactivity of the body poses a high risk of systemic inflammatory response to antitumor surgical treatment. This justifies the inclusion of extracorporeal detoxification into preoperative preparation of this category of patients as an active preoperative therapy.

Conclusions. Simultaneous elevation of LII, RNR and NLR characterizing the presence of endotoxicosis in sub- and decompensation of endogenous intoxication by own physiological detoxification systems requires an active preoperative preparation with extracorporeal detoxification.

Keywords: lung cancer, inflammatory complications, endogenous intoxication, body reactivity, extracorporeal detoxification, therapeutic plasma exchange

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Compliance with ethical standards: the ethical principles presented by the World Medical Association Declaration of Helsinki, 1964, ed. 2013 were observed in the study. The study was approved by the ethics committee of the National Medical Research Centre for Oncology (extract from the protocol of the meeting No. 19 dated 22/11/2021). Informed consent was received from all participants of the study

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ОРИГИНАЛЬНАЯ СТАТЬЯ

Клинико-патогенетическое обоснование к применению в комплексе предоперационной подготовки больных немелкоклеточным раком легкого, осложненным воспалительным процессом, терапевтического плазмообмена

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РЕЗЮМЕ

Цель исследования. Определить патогенетическую обоснованность и критерии показаний к включению в комплекс предоперационной подготовки больных немелкоклеточным раком легкого (НМРЛ), осложненным воспалительным процессом, методов экстракорпоральной детоксикации.
Пациенты и методы. В исследование включены данные историй болезни 222 больных первично выявленным НМРЛ I–IV стадий, поступивших на плановое хирургическое лечение в отделение торакальной онкологии ФГБУ «НМИЦ онкологии» Минздрава России в период 2017–2019 гг. Всем больным проводили оценку показателей эндогенной интоксикации – лейкоцитарного индекса интоксикации (ЛИИ), индекса резистентности организма (ИРО), реактивного ответа нейтрофилов (РОН), нейтрофильно-лимфоцитарного соотношения (НЛС). Также изучали показатели воспалительного ответа – интерлейкин-6 и прокальцитонин.
Результаты. Выявлено, что развитие воспалительных осложнений у больных НМРЛ наблюдается в 36,5 % случаев. Более чем у 70 % больных впервые диагностированным НМРЛ течение онкологического заболевания сопровождается выраженными клинико-лабораторными признаками эндогенной интоксикации с угнетением защитных систем гомеостаза. Наличие исходного эндотоксикоза в суб- или декомпенсированной форме на фоне снижения общей реактивности организма представляет высокий риск развития генерализованного воспалительного ответа на проведение противоопухолевого хирургического лечения. Это актуализирует включение в комплекс предоперационной подготовки данной категории больных экстракорпоральной детоксикации в качестве активной предоперационной терапии.
Заключение. Одновременное повышение показателей ЛИИ, РОН и НЛС, характеризующих наличие эндотоксикоза в условиях суб- и декомпенсации эндогенной интоксикации собственными физиологическими системами детоксикации, определяют необходимость проведения активной предоперационной подготовки с включением компонента экстракорпоральной детоксикации.

Ключевые слова: рак легкого, воспалительные осложнения, эндогенная интоксикация, реактивность организма, экстракорпоральная детоксикация, терапевтический плазмообмен

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Соблюдение этических стандартов: в работе соблюдались этические принципы, предъявляемые Хельсинкской декларацией Всемирной медицинской ассоциации (World Medical Association Declaration of Helsinki, 1964, ред. 2013). Исследование одобрено этическим комитетом ФГБУ «НМИЦ онкологии» Минздрава России (выписка из протокола заседания № 19 от 22.11.2021 г.). Информированное согласие получено от всех участников

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INTRODUCTION

To date, lung cancer (LC) occupies a leading position among all malignant neoplasms, representing a significant socio-economic problem in Russia and the world overall. In the Russian Federation, the increase in morbidity and mortality from LC is especially noticeable among the male population in the age group over 60 years, while 85 % of detected cases are represented by non-small cell lung cancer (NSCLC) [1]. Unfortunately, in more than 70 % of patients, a malignant neoplasm of the lung is diagnosed at the stage of a locally widespread process, or there is a metastatic lesion, including the pleura, the opposite lung, and the chest wall [2].

According to current data, the surgical method in combination with antitumor therapy significantly affects the prognosis of the disease, improving the survival of patients with NSCLC at virtually all stages compared with maintenance therapy [3]. At the same time, the nature of the course of the disease depends not only on the effectiveness of the method used, but also on the occurrence of severe complications that may cause the refusal of specialized care or restriction of full-fledged antitumor treatment.

It is fair to note that all cancer patients are susceptible to various infectious complications, which is 4–8 times more common than in the general population. This is due to a defect in the immune system, provoked by both tumor development and increased catabolic processes against the background of impaired physiological detoxification and excretion processes, as well as secondary changes in organs and tissues due to antitumor therapy [4]. In predicting complications, including septic ones, it is necessary to consider not only the primary infection of the tumor, but also the aggressive tactics of extended operations, including total removal of the organ affected by the tumor and suspected metastatic spots [5]. According to some data, the incidence of inflammatory pulmonary complications in patients with progressive NSCLC ranges from 12 to 40 %, and the mortality rate reaches 26.5–33 % [6]. These indicators are due to several reasons. Thus, endobronchial tumor growth leads to the formation of a secondary inflammatory focus in the lung tissue and in most patients, LC presents as pneumonitis, pleurisy, pleural empyema or lung abscess with pneumonia [7]. In addition, the late stages of LC are characterized by the disintegration of the tumor with the formation of necrosis and an inflammatory zone in the tissue of the affected lung. The necrotic focus becomes a source of intoxication, which is caused by the prolonged intake of cellular breakdown products into the blood [8].

The factors determining the prognosis of the functional state of patients with LC after radical surgical treatment, which involves total organ removal or extended lung resection with regional lymphadenectomy, should also include the features of ensuring gas exchange during surgery. The cessation of air circulation in the lung during surgery provokes a massive release of inflammatory cascade mediators into the bloodstream, and inadequate gas exchange with a decrease in oxygen partial pressure and a decrease in cardiac output cause the development of hypercapnia and tissue hypoxemia [9]. In addition, rotational surgical manipulations on a lung "turned off" from gas exchange contribute to aggravating the situation caused by the powerful release of tumor cell decay products into the general bloodstream, initiating the launch of a systemic inflammatory reaction, the development of acute lung damage in the early postoperative period [7].

In the conditions of the initial inflammatory process, surgical stress, accompanied by functional disorders of the sympathetic nervous system, paradoxical endocrine responses, as well as immunological and hematological changes, it promotes the activation of leukocytes, fibroblasts, endothelial cells, and platelets, followed by massive release of biologically active substances. A cascade of pathological changes and disruption of the normal functioning of the microcirculatory bed in patients with LC leads to the development and rapid progression of acute lung injury, as a result one in three patients dies [10].

Everything listed above determines the relevance of the concept of endotoxicosis correction and of prevention of acute respiratory distress syndrome in patients with NSCLC complicated by the inflammatory process that is already happening in the preoperative period. At the same time, the inclusion of extracorporeal detoxification in the complex of preoperative preparation, which ensures the removal of excessive concentrations of pathognomonic endogenous toxic substances, can probably contribute to improving the results of the inpatient period of care for this category of patients.

The purpose of the study was to determine the pathogenetic validity and criteria of indications for inclusion of therapeutic plasma exchange in the complex of preoperative preparation of patients with NSCLC complicated by the inflammatory process.

MATERIALS AND METHODS

The study included data obtained from the medical histories of 222 patients with primary NSCLC of stages I–IV who were admitted for elective surgical treatment at the Department of Thoracic Oncology of the National Medical Research Center of Oncology, in the period 2017–2019.

The median age in the study group was 61 years, the average age was 63.9 ± 1.7 years, the range was 37–78 years, with 77 % men and 23 % women. The age categories according to the criteria of the World Health Organization were represented by people: under 45 years – 2.3 % (*n* = 5), 45–59 years – 30.6 % (*n* = 68), 60–74 years – 61.7 % (*n* = 137), over 75 years – 5.4 % (*n* = 12). According to preliminary data of clinical examination and histological analysis of the surgical material, the staging of the tumor process was carried out (TNM classification 8-edition, 2017) [11]: $T_1N_0M_0$ in 6.3 % (*n* = 14), $T_{2a}N_0M_0$ in 26.6 % (*n* = 59), $T_{2b}N_0M_0$ in 8.1 % (*n* = 18), $T_3N_1M_0$ in 14.9 % (*n* = 33), $T_{3-4}N_{1-2}M0$ in 36.5 % (*n* = 81), $T_{3-4}N_3M_0$ in 6.7 % (*n* = 15), $T_{3-4}N_{2-3}M_1$ in 0.9 % (*n* = 2) patients. Morphological parameters of the tumor: the largest number was squamous cell carcinoma of varying degrees of differentiation, which was detected in 80.1 % of patients. According to the clinical and anatomical classification of RL, the following were presented: central cancer – 27.45 % (*n* = 61), peripheral cancer – 64.9 % (*n* = 144), peripheral cancer with centralization – 7.65 % of cases (*n* = 17). Surgical treatment included: lobectomy and bilobectomy – 67.9 % (*n* = 55), pneumonectomy – 8.7 % (*n* = 7), pleuropneumonectomy – 4.9 % (*n* = 4), combined pneumonectomy – 17.3 % (*n* = 14), pneumonectomy with tracheal bifurcation resection – in 1.2 % (*n* = 1) to the patient. Clinically significant concomitant diseases were identified: ischemic heart disease – 63.5 %, arrhythmias – 27.5 %, hypertension – 51.7 %, postinfarction cardiosclerosis – 22.9 %, chronic nonspecific lung diseases – 25.2 %, type 2 diabetes mellitus – 18.9 %, deep vein thrombophlebitis of the lower extremities – 28.4 %, gastric ulcer or 12 duodenum – 35.1 % of patients.

The control group consisted of 24 relatively healthy men and women without cancer, comparable in age and gender to the study group.

To diagnose the presence and nature of the course of endogenous intoxication (EI) accompanying the development of the oncological process, all patients upon admission were assessed according to leukogram data for indicators of endogenous intoxication – leukocyte intoxication index (LII), body resistance index (BRI), neutrophil reactive response (NRR), neutrophil-lymphocyte ratio (NLR). The indicators of the inflammatory response – interleukin-6 (IL-6) and procalcitonin (PCT) – were also studied. Criteria for inclusion of patients: primary diagnosed NSCLC in persons over 18 years of age. The exclusion criterion was under the age of 18, small cell lung cancer.

This study was approved by the Ethical Committee of the institution, It was also carried out the prior consent of patients to the processing of their personal clinical and laboratory data for scientific purposes (Protocol No. 19 of 11/22/2021).

The main material for this study was the blood (erythrocytes, plasma) of patients. Blood sampling was carried out in sterile vacuum tubes with preservative in the morning from the ulnar vein when patients were admitted to the hospital before any medical measures were carried out. A general clinical blood test was performed using the colorimetric method. The concentration of PCT was studied by the Brahms PCTQ test (Brahms Diagnostica, Germany), IL-6 in blood serum was determined by enzyme immunoassay (Vector-Best reagents, Novosibirsk).

Statistical verification of compliance with the normal distribution was carried out according to the Shapiro-Wilk and Kolmogorov-Smirnov W-criterion, the results are presented in the form of $M \pm m$ (M is the sample mean, m is the error of the mean, the median (*Me*), which in all groups practically did not differ from *M*, and the interquartile range in the form of a calculation of the lower and upper quartiles: (Q25 and Q75).

STUDY RESULTS

A retrospective analysis of the data from 222 medical histories showed that in 81 patients (36.5 %), the manifestation of cancer manifested clinical signs of the inflammatory process and was diagnosed as

paracancerous pneumonia in 11, pneumonitis in 62, pleuritis and pleural empyema in 8 cases. These patients formed the basis for further research.

An analysis of the data of 81 patients in whom the course of NSCLC was complicated by inflammatory complications indicated that 58 patients (71.6 %) were initially diagnosed with central LC, 6 patients (7.4 %) had a peripheral form and 17 patients (21.0 %) had peripheral cancer with centralization of the process. In the group with complications, 92.9 % (*n* = 75) of men and 7.1 % (*n* = 6) of women. According to age indicators, the group of patients in the age category 60–74 years prevailed 59.3 % (*n* = 48), then 45–59 years – 33.3 % (*n* = 27), at the age of 45 years and over 75 there were 3 patients (3.7 %). The complicated course was more often observed in patients with stage 3a – in 64.4 % (*n* = 52), then 2b – 21.1 % (*n* = 17), 3b – in 11.1 % (*n* = 9), stage 2a and stage 4 in 2 patients.

In 69 of 81 (85.2 %) patients, clinical signs of EI were noted, which had manifestations in the form of complaints of weakness and increased fatigue, fever with varying degrees of myalgia, sleep disorders and decreased psychoemotional activity, or a combination of these clinical signs of EI. When analyzing the white blood cell panel, it was revealed that upon admission, 63 out of 81 (77.7 %) patients had laboratory signs of EI due to tumor autolysis, and in some cases with the addition of bacterial infection – 22 (27.2 %) (Table 1).

It was noted that in 13 (16.0 %) patients with NSCLC with the development of mild EI, stability of the general reactivity of the body with a compensated state of homeostasis was observed. In 19 (23.5 %) patients, signs of mild EI were accompanied by inhibition of general reactivity, but the stability of homeostasis was ensured by detoxification systems of the body, the level of NRR was within physiological norms. In 10 (12.3 %) patients, a mild degree of EI was recorded with signs of inadequate compensation due to inhibition of the general reactivity of the body and instability of homeostasis – in addition to an increase in LII, an increase in the level of NRR and NLR was observed. In 21 (25.9 %) patients, an average degree of severity of EI was revealed with a marked decrease in BRI, a manifestation of subcompensation or decompensation of physiological detoxification systems, which was manifested by a significant increase in relative to normal values of neutrophil reactive response indicators.

Laboratory signs of initial systemic inflammation were revealed in 8 out of 81 (9.9 %) patients with initially diagnosed pleurisy and pleural empyema, according to IL-6 and PCT indicators. The serum concentration of PCT was 0.422 ± 0.15 ng/ml, exceeding the values of healthy people by 3.7 times ($p < 0.001$). The IL-6 values were 67.3 ± 4.1 pg/ml, which exceeded the normal values by 14.3 times ($p < 0.001$).

The probability that a full-fledged and radical surgical treatment in these patients in conditions of failure of homeostasis and protective systems of the body can provoke a further decrease in compensatory reactions with the subsequent development of systemic and organ dysfunctions. An analysis of the nature of the course of the early postoperative period in these patients showed that 28 out of 81 (34.6 %) patients were diagnosed with complications in the first three days after surgery – acute respiratory distress syndrome, pneumonia, sepsis, multiple organ failure. In all these patients, in the preoperative period, according to leukogram data, the presence of mild and moderate EI was recorded in combination with a decrease in overall reactivity and the state of sub- and decompensation of EI by physiological detoxification systems of homeostasis, an increase in NLR indicators, which amounted to 93.3 % of the total number of patients with initially identified disorders according to leukogram data (28 out of 30 patients). The hospital mortality rate in this cohort of patients was 28.6 % with a total mortality rate of 5 %.

The severity of postoperative complications and high mortality have determined the relevance of the development and implementation of the concept of reducing the risk of early post-surgical complications at the stage of the preoperative period.

DISCUSSION

In general, the data accumulated to date indicate that in the conditions of actively developing surgical technologies, personalization of targeted and radiotherapy, the long-term results of treatment of patients with NSCLC remain disappointing [12]. It is obvious that a locally widespread tumor process with an inflammatory component is the cause of a number of pathological transformations that can lead to severe systemic complications in patients with LC. The data obtained in the study indicate ini-

tially pronounced changes in the functional state of patients with NSCLC. Thus, in the preoperative period, 71.55 % of patients registered the tension of non-specific protective systems of the body with simultaneous detection of limited reserve capabilities of the immune system.

To obtain a complete picture of the initial state of protective, including physiological detoxification systems, we conducted a retrospective analysis of the medical histories of patients with NSCLC with the determination of the level of integral intoxication indices LII, NRR, BRI, NLR. The leukocyte intoxication index (LII is a characteristic indicator of tissue degradation processes and various levels of EI. In fact, the formula represents the absolute ratio of the number of neutrophilic leukocytes to lymphocytes, monocytes, eosinophils:

LII = (4 MC + 3 MMC + 2 RSN + SN) × (PC + 1) / (Lf + M) × (E + 1), where MC are myelocytes, MMC – metamyelocytes, RSN – rod-shaped neutrophils, SN –

Table 1. LII, NRR, BRI, NLR values in patients with NSCLC prior to the surgical intervention (*M ± m*)

Endogenous intoxication level	White blood cell panel indicators (U)			
	LII (with normal range 1–1.6 ± 0.2)	BRI (with normal range 50–100)	NRR (with normal range 10.6 ± 2.1)	NLR (with normal range 1–2.1 ± 0.1)
EI absence, stability of the general body reactivity (*n* = 18)	1.101 ± 0.307 1.004 (0.4; 2.112) *p* = 0.000000	89.82 ± 2.36 91.22 (82.24; 98.6) *p* = 0.014440	11.674 ± 1.31 11.4 (4.295; 18.95) *p* = 0.001268	1.262 ± 0.412 2.724 (1.1; 1.427) *p* = 0.011258
Mild EI. stability of the general body reactivity, physiologic EI compensation (*n* = 13)	1.603 ± 0.114 1.559 (1.1; 3.012) *p* = 0.01024	74.62 ± 3.32 76.42 (72.44; 81.5) *p* = 0.010140	13.684 ± 1.11 14.4 (12.999; 15.96) *p* = 0.001277	1.844 ± 0.611 1.661 (1.541; 1.997) *p* = 0.011001
Mild EI, decrease in the general body reactivity, physiologic EI compensation (*n* = 19)	3.603 ± 0.417* 3.154 (2.4; 5.232) *p* = 0.000000	49.55 ± 3.46 46.25 (44.43; 58.1) *p* = 0.021040	13.085 ± 1.62 12.4 (10.991; 16.75) *p* = 0.001441	2.242 ± 0.312 2.724 (1.7; 3.227) *p* = 0.011258
Mild EI, decrease in the general body reactivity, physiologic EI subcompensation. (*n* = 10)	3.422 ± 0.312* 3.214 (2.9; 5.889) *p* = 0.010102	41.09 ± 2.34* 42.34 (32.29; 48.4) *p* = 0.010630	19.24 ± 1.27 19.1 (18.399; 24.92) *p* = 0.001252	7.173 ± 0.227* 6.664 (6.2; 8.138) *p* = 0.011056
Moderate EI, decrease in the general body reactivity, physiologic EI compensation. (*n* =11)	3.206 ± 0.217* 2.812 (2.2; 5.435) *p* = 0.020101	36.22 ± 3.41* 35.33 (31.11; 46.1) *p* = 0.010442	36.22 ± 3.21* 35.22 (29.30; 47.11) *p* = 0.01102	9.402 ± 0.217* 9.661 (8.6; 10.286) *p* = 0.010256
The average degree of EI, a decrease in the overall reactivity of the body, the physiological inadequacy of EI compensation (*n* = 10)	3.992 ± 0.202* 3.913 (3.2; 6.204) *p* = 0.012135	21.88 ± 3.11* 20.24 (16.37; 24.2) *p* = 0.010625	28.11 ± 2.83* 26.93 (22.12; 36.4) *p* = 0.010331	13.453 ± 0.212* 13.254 (12.2; 15.931) *p* = 0.012401

Note: * – $p < 0.05$ compared to the indicators in healthy people. LII – Leucocytinc indicator of intoxicatin, NRR – neutrophil reactive response, BRI – body resistance index, NLR – neutrophil-lymphocytic ratio

segmented neutrophils, PC – plasma cells, Lf – lymphocytes, M – monocytes, E – eosinophils.

LII is one of the most common intoxication indices, the indicators of which are: norm – 0.62–1.6 U, mild degree of intoxication – 2.7–3.7 U; average degree 3.6–4.8 U; severe degree – 5.8–8.5; above 8.6 U – extremely severe degree of EI. An increase in LII indicators to 4–9 U indicates the presence of bacterial toxins, the interval from 2 to 3 U is an indicator of intoxication by autolysis products. In addition to LII, the body resistance index (BRI) is considered as an objective indicator of EI, which is calculated as the ratio of the number of leukocytes to the product of the patient's age by the LII coefficient.:

BRI = L (thousand/l) / patient's age × LII.

BRI indicators vary from 50 to 100 U. At the same time, low BRI numbers indicate the development of an acute septic process.

The neutrophil NRR is also an EI index and is equal to the product of the sum of myelocytes, young (a coefficient of 1 is added if the total is less than one) multiplied by the percentage of rod-shaped and segmented neutrophils divided by the product of the sum of the percentage of basophils, lymphocytes, and monocytes by the number of eosinophils.

NRR = ((MC + MMC +1) × RSN × SN) / ((Lf + B + M) × E), where MC are myelocytes, MMC – metamyelocytes, RSN – rod-shaped neutrophils, SN – segmented neutrophils, E – eosinophils, Lf – lymphocytes, M – monocytes, B – basophils. The normal values of NRR are 10.6 ± 2.2 rel. U. NRR level 15–25 rel. U. compensation of EI is indicated, 26 –40 rel. U – subcompensation, more than 40 rel. U – decompensation of the inflammatory process [13].

There is no doubt about the objectivism of evaluating EI indicators with the possibility of predicting the complicated course of the early postoperative period using integral intoxication indices calculated from a leukogram. Undoubtedly, this is an urgent and effective way that allows in a short time, according to a general blood test, to assess the initial state of the patient's homeostasis with the determination of EI and to develop tactics for necessary and timely treatment. In addition, according to modern data, the integral indicators of the neutrophil reactive response have a pronounced informative character. This criterion characterizes the effects of toxins on the change in the ratio index of cells with varying degrees of nuclear differentiation (rod-shaped and segmented neutrophils). Numerous studies have determined the role of the neutrophil-lymphocyte ratio as a marker of prognosis and severity of chronic diseases such as cirrhosis of the liver, cholecystitis, pancreatitis, chronic obstructive pulmonary disease, as well as in determining the risk of cardiovascular complications in cardiac surgery. The Russian and foreign literature reflects aspects of the dynamics of NLR indicators in oncology, which shows the prognostic significance of this indicator [14]. The role of activated neutrophils in the reactivity of the body determines the restructuring of metabolic processes, migration and adhesion, the formation of regulatory and secretory functions. A number of authors believe that an increase in NLR is one of the signs of activation of systemic inflammatory processes in patients with multiple organ dysfunction syndrome, in which, due to increased secretion of inflammatory mediators and cytokines, the role of neutrophils is important. Numerous clinical studies indicate a certain sensitivity of NLR for stratification of the systemic inflammatory response of the body in infection and bacteremia, which has an important prognostic value [15].

In addition, it is generally recognized that the course of the disease largely depends on the reactivity of the body, which is largely determined by the immune system. IL-6 and PCT levels are true and chronologically valuable biomarkers of the development of an inflammatory response. These indicators demonstrate a pronounced stimulation of immune reactions in the structure of the inflammatory response of the patient's body, which makes it possible to choose a rational and timely therapy tactic. The prognostic significance of the markers is determined by the fact that the increase in indicators indicates the development of an unfavorable course of the disease [16].

The coexistence of tumor and inflammatory processes in patients with NSCLC is associated with a significant increase in the number of postoperative complications, including inflammatory genesis, which, accordingly, worsens the prognosis and treatment outcomes of the hospital period of this category of patients. In the studied group of patients, the incidence of purulent-septic complications was 36.5 % of cases. We studied the nature of early postoperative complications in patients with NSCLC.

Of the 222 patients, 141 (63.2 %) had an uncomplicated course, and 81 (36.5 %) patients had a complicated course. Early postoperative complications were diagnosed in 28 (34.5 %) patients. At the same time, 34.6 % of these patients in the early postoperative period (the first 3 days after surgery) revealed the development of life-threatening complications: acute respiratory distress syndrome, pneumonia and others. It was revealed that the course of cancer in 81 patients with a complicated course of the malignant process was accompanied by the development of endogenous intoxication, determined by an increased level of LII and NLR. At the same time, only in 28 patients with a complicated course of the early postoperative period, a significant increase in the indicators of the neutrophil reactive response was recorded, characterizing the inadequacy of compensation for EI by physiological detoxification systems of homeostasis, in some cases in combination with a decrease in the reactivity of the body. In patients with severe postoperative complications, the values of inflammatory markers turned out to be indicative: the PCT content exceeded the normal limits by 3.7 times, and IL-6 by 14.3 times, which indicated systemic inflammation.

Taking into account the presence of endotoxicosis and systemic inflammatory response in the studied patients, the complex of standard preoperative preparation should be supplemented with extracorporeal detoxification. The choice of the therapeutic plasma exchange (TPE) method is justified by its maximum detoxification potential, which allows removing all types of toxic substances from the bloodstream, including those associated with proteins. During the TPE procedure, inflammatory mediators actively adhere from the systemic bloodstream to the filter membrane, which reduces the risk of generalized systemic inflammation and, as a result, acute damage to the lung parenchyma [17].

The study made it possible to establish that the manifestation of cancer in patients with stage I–IV LC is characterized by the presence of endogenous intoxication of varying degrees of compensation. In this regard, it is justified to conduct detoxification therapies in the preoperative period in patients with the manifestation of EI in combination with inhibition of the general reactivity of the body and instability of homeostasis. It is most likely that full-fledged and radical surgical treatment in these conditions can provoke a further decrease in the compensatory potential of homeostasis with the subsequent development of systemic disorders, which justifies the need for active preoperative preparation of patients with NSCLC aimed at preventing severe inflammatory complications.

An example of the development of life–threatening complications in this category of patients is the clinical case of treatment of a patient with acute damage to a single lung after radical surgery – pneumonectomy, described by us in 2020 [18]. The presented clinical example demonstrates the severe course of the postoperative period in a patient 67 years after radical surgical treatment for cancer of the lower lobe of the left lung $cT_3N_0M_0$ art. II, with disintegration and abscessing paracancerous pneumonia, a condition after 3 courses of polychemotherapy. The scope of the operation included an extended combined pneumonectomy on the left, resection of the left atrium, resection of the pericardium, partial pleurectomy, plastic pericardium with polypropylene mesh. The severity of the patient's condition was due to the development of generalized inflammation with acute damage to a single lung on the 1st day of the postoperative period. Respiratory function was compensated by artificial lung ventilation (LV) (Hamilton G5 device). Ventilation parameters: respiratory rate – 16 v min.; airway pressure – 10 cm of water; positive pressure at the end of exhalation (Positive pressure at the end of exhalation – PEEP) – 5 cm of water; fraction of oxygen in the inhaled air (Fraction of Inspired Oxygen – FiO_2) – 80 %; respiratory volume – 330 ml; minute volume of respiration – 5.5 l/min. Against this background, SpO_2 is 90 %. Indicators of acid-base state: partial pressure of carbon dioxide in arterial blood (pCO_2) 36.5 mmHg; partial pressure of oxygen in arterial blood (pO_2) 114 mmHg; pH 7.43; base deficit (BE) 0.2; bicarbonate ($HCO_{3.}$) 32.4 mmol/L. According to blood tests: leukocytosis 32 × 10^9/l; neutrophilosis 80 %; leukocyte activity of endotoxin – 0.67 (Response – 0.92); PCT – 46 ng/ml; IL-6–1860 pg/ml. X-ray examination data: inflammatory infiltration in the lower lateral sections of the only lung. The probability of death on the MPM II scale (Mortality prediction model) was 75.3 %, which required a complex of high-tech intensive treatment with the inclusion of an extracorporeal detoxification program. In this case, the outcome of the hospital treatment period was favorable, the patient was discharged

from the hospital. Saving the life of this patient became possible with full-fledged treatment, timely inclusion in the treatment complex of extracorporeal detoxification. At the same time, it is possible that active preoperative preparation aimed at relieving the severity of EI and optimizing the functional state of the body's own physiological detoxification systems in the preoperative period could prevent the development of such a formidable complication in the postoperative period. However, this dictates the need for confirmation and, therefore, further research.

CONCLUSIONS

It was revealed that the development of inflammatory complications in patients with NSCLC is observed in 36.5 % of cases. In conditions of a combination of a tumor disease and an inflammatory component, a decrease in the compensatory capabilities of the patient's body can be expected with a high degree of probability and, as a result, the development of inflammatory complications of varying severity in the early postoperative period. The data obtained demonstrate that in more than 70 % of patients with newly diagnosed NSCLC, the course of cancer is accompanied by pronounced clinical and laboratory signs of EI with inhibition of protective homeostasis systems.

The presence of initial endotoxicosis in a sub- or decompensated form against the background of a decrease in the general reactivity of the body poses a high risk of developing a generalized inflammatory response to antitumor surgical treatment. This actualizes the inclusion of extracorporeal detoxification as an active preoperative therapy in the complex of preoperative preparation of this category of patients.

The simultaneous increase in the indicators of LII, NRR and NLR, characterizing the presence of endotoxicosis in conditions of sub- and decompensation of EI by their own physiological detoxification systems, determine the need for active preoperative preparation with the inclusion of a component of extracorporeal detoxification, i. e. therapeutic plasma exchange.

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Ushakova N. D. – performed writing of the draft;
Rozenko D. A. – performed scientific editing;
Tikhonova S. N. – initiated formulation of the research goal, analysis of the results;
Kharagezov D. A. – carried out the development of the research design;
Popova N. N. – provided with clinical support of the study.

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ORIGINAL ARTICLE

MicroRNA-34, microRNA-130, microRNA-148, microRNA-181, microRNA-194 and microRNA-605 expression in colon cancer tissue

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ABSTRACT

Purpose of the study. Determination of the expression of microRNA-34, microRNA-130, microRNA-148, microRNA-181, microRNA-194 and microRNA-605 in colon tumor tissue depending on the clinical and morphological features of the tumor and the effectiveness of treatment.
Materials and methods. The study included 56 patients diagnosed with colorectal cancer aged 43 to 75 years with the average age of 54 years. Taking into account the local prevalence of the process patients received surgical or combined treatment, including neoadjuvant chemotherapy, in the clinics of the Cancer Research Institute, Tomsk NRMC. MicroRNA expression was determined by polymerase chain reaction (PCR) in real time.
Results. The obtained information revealed the relation of microRNA-130 to the tumor size. The development of regional metastases was associated with changes in microRNA-130, microRNA-194 and microRNA-605. The level of histological organization of the tumor was associated with microRNA-34, microRNA-130, microRNA-148, and the response to therapy – with microRNA-130, microRNA-148 and microRNA-605. In addition, according to the study, the significance of microRNA-130 was revealed, which is associated with tumor spread, histological differentiation and response to antitumor therapy.
Conclusion. The features of expression of microRNA-34, microRNA-130, microRNA-148, microRNA-181, microRNA-194 and microRNA-605 associated with clinical and morphological features of colon tumors were revealed. Correlations between the studied indicators are noted, which probably determine the outcome and prognosis of the disease.

Keywords: colorectal cancer, microRNA-34, microRNA-130, microRNA-148, microRNA-181, microRNA-194, microRNA-605, prevalence of the disease, treatment effect

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Compliance with ethical standards: the ethical principles presented by the World Medical Association Declaration of Helsinki, 1964, ed. 2013 were observed in the study. The study was approved by the ethics committee of Cancer Research Institute, Tomsk NRMC (extract from the protocol of the meeting No. 22 dated 28/11/2022). Informed consent was received from all participants of the study

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ОРИГИНАЛЬНАЯ СТАТЬЯ

Экспрессия микроРНК-34, микроРНК-130, микроРНК-148, микроРНК-181, микроРНК-194 и микроРНК-605 в ткани опухоли ободочной кишки

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РЕЗЮМЕ

Цель исследования. Определение экспрессии микроРНК-34, микроРНК-130, микроРНК-148, микроРНК-181, микроРНК-194 и микроРНК-605 в ткани опухоли ободочной кишки в зависимости от клинико-морфологических особенностей опухоли и эффективности лечения.

Материалы и методы. В исследование было включено 56 пациентов с диагнозом колоректальный рак в возрасте от 43 до 75 лет (средний возраст составил 54 года). Пациенты получали хирургическое или комбинированное лечение, включая неоадъювантную химиотерапию с учетом местной распространенности процесса, в клиниках НИИ онкологии Томского НИМЦ. Экспрессию микроРНК определяли методом полимеразной цепной реакции (ПЦР) в реальном времени.

Результаты. Получены данные о связи микроРНК-130 с размером опухоли. Развитие регионарных метастазов было ассоциировано с изменением микроРНК-130, микроРНК-194 и микроРНК-605. Уровень гистологической организации опухоли был связан с микроРНК-34, микроРНК-130, микроРНК-148, а ответ на терапию – с микроРНК-130, микроРНК-148 и микроРНК-605. Кроме того, по данным исследования была выявлена значимость микроРНК-130, которая связана с распространением опухоли, гистологической дифференцировкой и ответом на противоопухолевую терапию.

Заключение. Выявлены особенности экспрессии микроРНК-34, микроРНК-130, микроРНК-148, микроРНК-181, микроРНК-194 и микроРНК-605, ассоциированные с клинико-морфологическими особенностями опухоли ободочной кишки. Отмечены корреляционные зависимости между исследуемыми показателями, которые, вероятно, определяют исход и прогноз заболевания.

Ключевые слова: колоректальный рак, микроРНК-34, микроРНК-130, микроРНК-148, микроРНК-181, микроРНК-194, микроРНК-605, распространенность заболевания, эффект лечения

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Соблюдение этических стандартов: в работе соблюдались этические принципы, предъявляемые Хельсинкской декларацией Всемирной медицинской ассоциации (World Medical Association Declaration of Helsinki, 1964, ред. 2013). Исследование одобрено Комитетом по биомедицинской этике при НИИ онкологии Томского НИМЦ (выписка из протокола заседания № 22 от 28.11.2022 г.). Информированное согласие получено от всех участников исследования

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Конфликт интересов: все авторы заявляют об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи

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INTRODUCTION

Epigenetic regulation is a powerful factor determining the molecular features of tumor growth and has a significant impact on the effectiveness of antitumor treatment [1]. Colon cancer ranks 6th in the world in terms of prevalence and 3rd among the most significant malignant tumors in the Russian Federation [2], which is associated with the activation of significant signaling cascades.

Currently, the features of epigenetic regulation, particularly the importance of microRNAs, in the development of colon tumors have been little studied [3]. It is believed that microRNA-34 and microRNA-34a exhibit oncosuppressor properties, which is associated with the effect on the p53 protein and on the state of intracellular signaling cascades (IL-6R/STAT3 and PI3K/AKT/mTOR) [4, 5]. Recent studies have shown that representatives of the microRNA-148/152 family become attractive biomarkers to predict the biological behavior of tumors of various origins [6].

Another significant indicator is microRNA-194, which determines the features of oncogenesis in colorectal cancer [7, 8]. This fact is related to the regulatory effect of microRNA-194 on the activity of the MAP4K4/c-Jun/MDM2 signaling cascade, where it manifests itself as an oncosuppressor [3].

It is known that activation of the proteasome system accompanies the development of colon tumors [9]. microRNA-605 has been shown to be able to influence PSMD10, the ATP-independent subunit of proteasomes or gankyrin, determining, among other things, the risk of liver metastases [10].

There is practically no information about the role of microRNAs 130 and 181 in the development of colon cancer. It is known that high expression of the miRNA-130 family can predict an unfavorable prognosis in cancer patients [11]. Reduced expression of microRNA-130–5p in lung cancer tissues and cells contributed to the metastasis and invasion of this tumor due to EZH2 (Enhancer of zeste homolog 2) [12].

Recent studies have shown that representatives of the microRNA-181 family regulate significant intracellular processes: in cell proliferation, apoptosis, autophagy, angiogenesis, and drug resistance. In addition, it has been demonstrated that the presented microRNAs exhibit their regulatory effects by modulating a variety of signaling pathways, including the PI3K/AKT, intracellular signaling pathway MAPK (MAPK), transforming growth factor beta (TGF-b), intracellular signaling pathway Wnt (Wnt), transcription factor κB (NF-κB), intracellular signaling pathway Notch (Notch) [13].

Currently, a panel of microRNAs is known, including more than 10 microRNAs, including microRNA-34 and microRNA-148, which are associated with the development of resistance to antitumor drugs [14], but its diagnostic value is practically unknown.

The purpose of the study was to determine the dependence of the clinical and morphological features of the tumor and the effectiveness of treatment on the expression of microRNA-34, microRNA-130, microRNA-148, microRNA-181, microRNA-194 and microRNA-605 in colon tumor tissue.

MATERIALS AND METHODS

The study included 56 patients diagnosed with colorectal cancer aged 43 to 75 years (the average age was 54 years). The patients received combined treatment, including neoadjuvant chemotherapy at the clinics of the Cancer Research Institute, Tomsk NRMC. Treatment was carried out according to the following scheme: 8 courses of neoadjuvant polychemotherapy according to the FolFox-6 scheme, including administration on the first day: oxaliplatin 85 mg/m^2 2-hour infusion, calcium folinate 400 mg/m^2 IV for 2 hours followed by a bolus of 5-fluorouracil 400 mg/m^2 IV jet and 46-an hour infusion of 5-fluorouracil 2400 mg/m^2 (1200 mg/m^2 / day) with an interval between courses of 14 days. Eighteen patients had the disease stage T2, 14 patients – T3 and 24 people – T4. The presence of regional metastases (N1–2) was recorded in 26 patients. Low grade tumors were detected in 44 patients, high grade in 12 patients. Partial regression of the tumor was noted in 46 patients and stabilization in 10.

The conduct of this work was approved by the Ethical Committee of the Cancer Research Institute, Tomsk NRMC. All procedures involving patients were carried out in accordance with the Protocol of the Helsinki Declaration on Human Rights (1964), Protocol No. 22 of 11/28/2022.

The research material was samples of the central part of the tumor and unchanged colon tissue obtained during surgical treatment, which were stored at a temperature of –80 °C.

Isolation of microRNAs

microRNA isolation was performed using a kit for isolation of total RNA and microRNA from the Lyra reagent (Biolabmix, Russia), combining methods of phenol-chloroform extraction of nucleic acids and their selective sorption on a silicon membrane, where lysis of the sample occurs in the Lyra reagent containing phenol and guanidine thiocyanate. The quality and integrity of the isolated nucleic acids were evaluated using capillary electrophoresis on a TapeStation device (Agilient Technologies, USA). The RIN ranged from 2.2–3.3.

MicroRNA reverse transcription was performed using a set of reagents from M-MuLV–RH. The selected set represents a complete system for the effective synthesis of the first chain of cDNA with mRNA or total RNA matrices (Biolabmix, Russia).

Quantitative polymerase chain reaction (PCR) with real-time reverse transcription

The level of gene expression was assessed using quantitative real-time reverse transcriptase PCR (RT-qPCR) on an iCycler amplifier (DTprime, DNA technology, Russia). To obtain cDNA on an RNA matrix, a reverse transcription reaction was performed using the OT m-MuLV-RH kit (Biolabmix, Russia) with random hexanucleotide primers in accordance with the instructions for the kit. PCR was performed in three replicas with volumes of 25 µl, containing 12.5 µl of HS-qPCR SYBR Blue BioMaster (Biolabmix, Russia), 300 nM of direct, reverse and RT primers and 50 ng of cDNA. PCR primers: Hsa-miR-34a-5p:
F: 5'-CGCGTGGCAGTGTCTTAGCT-3';
R: 5'-AGTGCAGGGTCCGAGGTATT-3';
RT Primer: 5'-GTCGTATCCAGTGCAGGGTCCGAG GTATTCGCAC TGGATACGACACAACC-3;
Hsa-mir-130a: F: 5'- GCCGCCAGTGCAATGTTAAA-3';
R: 5'- GTGCAGGGTCGGAGGT –3';
RT primer: 5'-GTCGTATCCAGTGCAGGGTCCGAGG-TATTCGCACTGGATACGACATGCCCT-3';
miR-148a-3p: F: 5'-TGCGCTCAGTGCACTACAGAAC-3';
R: 5'- CCAGTGCAGGGTCCGAGGTATT-3';
miR-181a: F: 5'- CGAACATTCAACGCTGTCG;
R: 5'- AGTGCAGGGTCCGAGGTATT-3';
RT primer: 5'-AACATTCAACGCTGTCGGTGAGTGTC-GTATCCAG TGCGAATACCTCGGACCCTGCACTGGA-TACGAC-3';
Hsa-mir-194 F: 5'-CACGCATGTAACAGCAAC-3';
R: 5'-CCAGTGCAGGGTCCGAGGTA-3';
RT-primer: 5`-GTCGTATCGAGAGCAGGGTCCGAGG-TATT CGCACTCGATACGACTC CACAT-3`;
Hsa-mir-605: F: 5'-TGCGGTAAATCCCATGGTG-CCTTC-3';
R: 5'-CCAGTGCAGGGTCCGAGGT-3';
RT: 5'-GTCGTATCCAGTGCAGGGTCCGAGGTGCACT-GGATACGACAGGAGAAG-3';
U6: F 5'-CTCGCTT CGGCAGCACATATACT-3',
R 5'-ACGCTTCACGAATTTGCGTGTC-3',
RT primer 5'-AAAATATGGAACGCTTC ACGAATTTGG-3.

Real-time PCR

The two-step amplification program included 1 cycle of 94 °C, 10 minutes of pre-denaturation; 40 cycles of 1st step 94 °C, 10 seconds and 2 step 20 seconds – at a temperature of 60 °C. To quantify the level of microRNA expression, the method of relative determination of quantitative values of $2-\Delta\Delta Ct$ was used. The expression of small nuclear RNU6 RNA was used as an endogenous control.

Statistical processing of the results was carried out using the Statistica 12.0 software package. Data validation for the normality of the distribution was performed using the Kolmogorov-Smirnov criterion. The values of gene expression are presented in conventional units of expression (relative units) as Me (Q1; Q3). The Mann-Whitney test was used to assess significant differences. The differences were considered significant at $p < 0.05$. Spearman's criterion was used in the correlation analysis.

STUDY RESULTS

It was revealed that the expression of microRNA-130 increased with increasing depth of invasion of the primary tumor (Table 1). At the same time, the appearance of regional metastases was associated with an increase in the expression of microRNA-130 by 1.9 times, while a decrease in the degree of tumor differentiation was accompanied by a decrease in the expression of this indicator. An increase of this indicator was recorded by 28.2 times with stabilization of the tumor process compared with patients with partial regression.

A similar picture with respect to the invasive potential of the tumor was obtained for microRNA-148, whose expression increased with a decrease in the degree of differentiation, as well as with a decrease in the tumor response to treatment in patients with

stabilization of the process, a 9.3-fold lower level of expression was noted compared with patients who achieved partial regression.

The opposite data were obtained for microRNA-194, which decreased by 3.2 times in the case of regional metastases. At the same time, an increase in the expression of the indicator was combined with a decrease in the degree of histological organization of the tumor and with a decrease in the effect of the tumor on treatment. This indicator was reduced by 7.2 times.

The expression of microRNA-605 in the tumor was 2.0 times higher in the presence of regional metastases compared with localized tumor variants. At the same time, in the case of highly differentiated tumors, the lowest indicators were noted, and in high grade carcinoma, the expression of the indicator was increased by 12.1 times compared with the above-described patients. An increase of 60.3 times was recorded for patients with a reduced response to therapy.

The association of histological differentiation of the tumor with microRNA expression was also con-

Table 1. MicroRNA-34, microRNA-130, microRNA-148, microRNA-181, microRNA-194 and microRNA-605 expression in colon cancer tissue, Me (Q1; Q3)

	N	MicroRNA-34, U	MicroRNA-130, U	MicroRNA-148, U	MicroRNA -181, U	MicroRNA -194, U	MicroRNA -605, U
T stages							
T2	18	0.15 (0.00; 0.46)	0.06 (0.00; 0.11)$^{\$}$	0.53 (0.27; 0.93)	0.00 (0.00; 0.00)	0.47 (0.12; 0.66)	0.12 (0.00; 0.87)
T3	14	0.03 (0.00; 0.93)	0.33 (0.00; 0.93)$^{\$}$	1.14 (0.38; 1.74)	0.00 (0.00; 0.00)	1.07 (0.00; 2.83)	2.46 (0.00; 2.83)
T4	24	0.37 (0.00; 1.35)	0.94 (0.52; 4.77)$^{\$}$	1.28 (0.59; 2.30)	0.00 (0.00; 0.00)	0.73 (0.47; 1.43)	1.04 (0.39; 11.79)
N stages							
N0	30	0.35 (0.00; 0.71)	0.43 (0.06; 1.74)	0.93 (0.27; 1.74)	0.00 (0.00; 0.00)	0.71 (0.27; 2.83)	0.87 (0.00; 21.11)
N1-2	26	0.15 (0.00; 4.00)	0.81 (0.11; 3.48)*	1.15 (0.61; 2.00)	0.00 (0.00; 0.00)	0.22 (0.00; 0.43)*	1.74 (0.19; 2. 64)*
Tumor tissue grade							
Low grade	44	0.44 (0.02; 1.35)	0.87 (0.47; 2.61)	1.37 (0.23; 1.78)	0.00 (0.00; 0.00)	0.65 (0.00; 1.31)	0.87 (0.39; 17.41)$^{\$\$\$}$
High grade	12	0.04 (0.00; 0.07) **	3.25 (0.00; 6.50)**	11.13 (1.14; 21.11)**	0.00 (0.00; 0.00)	6.73 (1.23; 12.23)**	10.56 (0.00;21.11)**
Therapy efficiency							
Local regression	46	0.09 (0.00; 0.62)	0.23 (0.03; 0.84)	0.97 (0.19; 1.28)	0.00 (0.00; 0.00)	0.68 (0.06; 0.99)	0.35 (0.00; 1.81)
Stabilisation	10	0.07 (0.00; 5.66)	6.5 (0.50; 14.93)$^{\#}$	9.19 (2.14; 21.11)$^{\#}$	0.00 (0.00; 0.00)	4. 92 (0.00; 12.23)$^{\#}$	21.11 (0.20; 32.0)$^{\#}$

Note: * – significance of differences compared with patients without regional metastases, $p < 0.05$; ** – significance of differences compared with patients with low grade tumors, $p < 0.05$; $^{\#}$ – significance of differences compared with patients with partial regression, $p < 0.05$;
$^{\$}$ – significance of differences according to the Kruskal criterion-Wallis, $p < 0.05$

firmed for microRNA-34, the expression of which was increased by 11.0 times in low-grade carcinoma tissue.

As a result of the correlation analysis, positive associations were noted between the studied indicators (Table 2). However, no correlation dependencies were found between microRNA-34 and microRNA-148.

DISCUSSION

During the study, data on the microRNA-130 link to the depth of tumor invasion were noted. There is evidence of the relationship of this indicator with the prognosis of the disease in cancer patients [11]. The development of regional metastases was associated with changes in microRNA-130, microRNA-194 and microRNA-605. At the same time, tumor aggressiveness was associated with low expression of microRNA-194, which is associated with activation of the MAP4K4/c-Jun/MDM2 signaling chain [3].

The level of histological organization of the tumor was associated with microRNA-34, microRNA-130, microRNA-148, and the response to therapy with microRNA-130, microRNA-148 and microRNA-605. microRNA-34 is believed to be an oncosuppressor [15, 16], therefore, the low level of the indicator was associated with high grade carcinomas. It is known that microRNA-148 is a universal marker of the biological behavior of tumors of various origins [6], and microRNA-605 can modify the PSMD10 protein, gankyrin, and participate in the formation of invasive tumor potential [10].

Despite the importance of the miR-181 family in controlling of cell proliferation, apoptosis, autophagy, angiogenesis, and drug resistance [16, 17], microRNA-181 expression was not detected in tumor tissue. There were also no correlations between microRNA-34 and microRNA-148 included in the model for predicting the effectiveness of antitumor treatment [18, 19]. The information received probably requires further study.

In addition, according to the study, the significance of microRNA-130 was revealed, which is associated with tumor spread, histological differentiation and response to antitumor therapy [20, 21]. Consequently, the importance of epigenetic regulation in the development of malignant neoplasms is associated with their involvement in the activation of significant signaling cascades, for example, PI3K/AKT, MAPK, TGF-b, Wnt, NF-κB, Notch [21], as well as growth and transcription factors [22].

Table 2. Analysis of link between the expression of microRNA-34, microRNA-130, microRNA-148, microRNA-181, microRNA-194 and microRNA-605 in colon tumor tissue

	Spearman's Coefficient, R	t(N-2)	*p*
MicroRNA-34 & MicroRNA -130	0.493	4.169	0.001
MicroRNA K-34 & MicroRNA -148	0.162	1.207	0.232
MicroRNA -34 & MicroRNA -194	0.359	2.828	0.006
MicroRNA -34 & MicroRNA -605	0.495	4.189	0.001
MicroRNA -130 & MicroRNA-148	0.547	4.805	0.003
MicroRNA -130 & MicroRNA -194	0.409	3.298	0.001
MicroRNA -130 & MicroRNA -605	0.688	6.975	0.000
MicroRNA -148 & MicroRNA -194	0.640	6.134	0.000
MicroRNA -148 & MicroRNA -605	0.540	4.725	0.000
MicroRNA -194 & MicroRNA -605	0.458	3.788	0.003

Notes: *p* – the significance of the differences

CONCLUSION

Thus, epigenetic regulation is important in the development of malignant neoplasms. The expression features of microRNA-34, microRNA-130, microRNA-148, microRNA-181, microRNA-194 and microRNA-605 links to the clinical and morphological features of colon tumors were revealed. microRNA-130 is a promising indicator that determines tumor development and response to treatment. The absence of microRNA-181 in colon cancer tissue has been shown, which undoubtedly requires further study. There was an increase in the expression of microRNA-34 in low grade tumors.

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ORIGINAL ARTICLE

Evaluation of engraftment and growth dynamics of orthotopic and heterotopic *in vivo* models of human breast cancer

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ABSTRACT

Purpose of the study. This work was to assess the engraftment and growth dynamics of breast cancer xenografts during orthotopic and subcutaneous injection using various types of biological material, as well as to develop an adequate model of breast cancer for further research.

Materials and methods. We used a disaggregated fragment of a tumor obtained from the patient, a certified breast cancer cell line VT20 – human breast carcinoma; a primary human breast carcinoma cell line. Female immunodeficient mice of the Balb/c Nude line in the amount of 36 animals were used as recipient animals. The subcutaneous and orthotopic models of breast cancer were developed in this project. Tumor growth was observed for 28 days from the moment of injection and tumor nodes were measured 2 times a week until the end of the experiment. Results were assessed using medians and percentiles. The nonparametric Mann-Whitney test was used to assess the significance of differences.

Results. The dynamics of the growth of tumor cells when injected into various sites was determined in the process of this work. The most successful in terms of a subcutaneous injection was the injection of tumor cells of the certified VT20 line. By the end of the experiment, the median tumor node of this group was 100.32 mm³. The analysis revealed tumor dynamics with orthotopic injection of tumor material, and the median volume of the tumor node in the group with the passport culture cell VT20 and the primary culture cell reached the same value – 149.22 and 148.25. mm³. It was found that both the cell line and the cell suspension were injected into tumor nodes that reached a significantly larger volume when injected orthotopically.

Conclusion. We have obtained a tumor model of breast cancer using various methods of material implantation and with the possibility of further use in testing new pharmacological substances.

Keywords: breast cancer, xenograft, Balb/c Nude, carcinoma, VT20, primary tumor, cell line

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ОРИГИНАЛЬНАЯ СТАТЬЯ

Сравнительная характеристика ортотопической и гетеротопической моделей *in vivo* рака молочной железы человека

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РЕЗЮМЕ

Цель исследования. Оценка приживления и динамики роста ксенографтов рака молочной железы (РМЖ) при ортотопической и подкожной инъекции с использованием различных типов биологического материала, а также разработка адекватной модели РМЖ для дальнейших исследований.

Материалы и методы. Использовали дезагрегированный фрагмент опухоли, полученной от пациентки, паспортизированную клеточную линию РМЖ ВТ20 – карцинома молочной железы человека; первичную клеточную линию карциномы молочной железы человека. В качестве животных-реципиентов использовали самок иммунодефицитных мышей линии Balb/c Nude в количестве 36 голов. В работе были разработаны подкожные и ортотопические модели РМЖ. Наблюдали рост опухоли в течение 28 суток с момента инъекции и осуществляли замеры опухолевых узлов 2 раза в неделю до конца эксперимента. Результаты оценивали с использованием медианы и процентилей. Для оценки достоверности различий использовали непараметрический критерий Манна-Уитни.

Результаты. В ходе данной работы была определена динамика роста опухолевых узлов при инъекции в различные сайты. Наиболее успешной, при подкожной инъекции, являлась инъекция опухолевых клеток, паспортизированной линии ВТ 20. На момент окончания эксперимента медиана опухолевых узлов данной группы составила 100,32 мм³. При анализе динамики роста опухоли при ортотопической инъекции опухолевого материала было выявлено, что в медиана объема опухолевых узлов в группе с паспортизированной культурой клеток ВТ20 и первичной культурой клеток достигала сходных значений – 149,22 и 148,25 мм³. Было выявлено, что как при инъекции клеточных линий, так и клеточной суспензии опухолевые узлы достигали значимо большего объема при ортотопической инъекции.

Заключение. Нами была получена опухолевая модель РМЖ при различных способах имплантации материала и с возможностью дальнейшего использования при тестировании новых фармакологических субстанций.

Ключевые слова: рак молочной железы, ксенографт, Balb/c Nude, карцинома, ВТ20, первичная опухоль, клеточная линия

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Соблюдение этических стандартов: все манипуляции в ходе эксперимента были выполнены с соблюдением этических принципов, установленных Европейской конвенцией о защите позвоночных животных, используемых для экспериментов или в иных научных целях (ETSN 123, Страсбург, 18 марта 1986 г). Протокол исследования № 19/123 от 3.08.2021 г. был одобрен локальным этическим комитетом ФГБУ «НМИЦ онкологии» Минздрава России. Пациенткой было предоставлено письменное согласие на передачу биологического материала

Финансирование: финансирование данной работы не проводилось

Конфликт интересов: все авторы заявляют об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи

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INTRODUCTION

Breast cancer (BC) is one of the most common cancers in the world. So in 2022, about 68 thousand new cases of this disease were registered in Russia [1]. According to global statistics, the incidence of BC is 11.6 % of all cancer cases, and about 626,000 deaths from BC, which accounted for 6.6 % of reported deaths [2]. In addition, this disease is highly heterogeneous and is divided into 4 different molecular subtypes, differing in the genomics of the tumor and the type of cells from which the tumor is initiated. So these subtypes include luminal A, luminal B, Her2-positive and triple negative BC [3]. To study different subtypes, scientists use several types of model systems: in silico, in vitro and in vivo [4]. Each of these methods has a number of advantages and disadvantages. Using the in silico model system, scientists are searching for potential target antigens and analyzing transcriptomic data [5], analysis of the relationship between genotype and phenotype to search for a gene as a promising target for therapy, as well as the search for directly or indirectly related genes selected as an alternative to the found target [6] and computer prediction of the complementarity of the binding region between the drug and the therapeutic target against BC [7]. When using the in vitro system, researchers analyze the mechanisms of resistance of tumor cells to drugs, evaluate the effect of new pharmacological substances on the viability of tumor cells [8], the mechanisms of organotoxicity of drugs are being investigated [9] and so on. Currently, the development of BC tumor models in vivo is also relevant in order to study biomarkers of tumor sensitivity to drugs, study new treatment regimens, and study the development of tumors in the body [10].

The purpose of the study was to evaluate the engraftment and growth dynamics of BC xenografts during orthotopic and subcutaneous implantation using various types of biological material, as well as to develop an adequate BC model for further research.

MATERIALS AND METHODS

Tumor material

For this work, we used a disaggregated fragment of a tumor obtained from a patient E. 75 years old, with digested breast cancer cT4N2Mo St IIIB, a certified BC VT20 cell line – human breast carcinoma; a primary human breast carcinoma cell line. The patient provided written consent for the transfer of biological material.

The cell lines were cultured in RPMI-1640 nutrient medium with the addition of fetal bovine serum (FBS), in a CO_2 incubator at a temperature of 37 °C and 5 % carbon dioxide content. To obtain the primary line, the tumor fragment obtained from the patient was placed in a nutrient medium with the addition of gentamicin (10 %), after which it was treated with ethyl alcohol (70 %). The fragment was crushed, centrifuged for 2 minutes at 3000 rpm, and then treated with collagenase solution. The resulting suspension was cultured in a CO_2 incubator, after which the cells were filtered and centrifuged for 2 minutes at 3000 rpm. Next, the suspension was washed with sterile DMEM with 5 % FBS, transferred to a T25 vial in 5 ml of DMEM + 10 % FBS medium. and the cells were cultured using the method described above. To obtain a suspension of cells from xenograft, a fragment of tumor tissue obtained from the patient was washed in a nutrient medium with an antibiotic (gentamicin), cleaned of necrosis fragments, connective tissue and blood vessels. After purification, the tumor fragment was crushed in a tissue disaggregation system using the automated BD Medimachine system (BD, USA) by adding 1 ml of RPMI-1640 nutrient medium. After crushing the tumor tissue, the resulting suspension was selected and filtered through nylon filters with a cell diameter of 70 microns and the resulting suspension of BC cells was injected into the nutrient medium of experimental animals.

Recipient animals

Female mice of the Balb/c Nude line in the amount of 36 heads, weighing 20–22 grams, aged 4 weeks, were used as recipient animals, purchased at the Scientific Research Institute "Nursery of Laboratory Animals" of the FIBH RAS. The animals were kept in SPF conditions of the testing laboratory center of the NMRC for Oncology, Ministry of Health of the Russian Federation, in individually ventilated cages at a temperature of 21–23 °C, with free access to water and feed. The animals were divided into 6 groups of 6 mice each. In group 1, there were animals with subcutaneous injection of a disaggregated tumor frag-

ment; group 2 – subcutaneous injection of VT20 cell culture; group 3 – subcutaneous injection of primary cell culture; group 4 – orthotopic injection of a disaggregated tumor fragment; group 5 – orthotopic injection of VT20 cell culture; group 6 – orthotopic injection of primary cell culture.

All manipulations during the experiment were performed in compliance with the ethical principles established by the European Convention for the Protection of Vertebrate Animals Used for Experiments or Other Scientific Purposes (ETSN 123, Strasbourg, March 18, 1986). Study Protocol No. 19/123 dated 08/3/2021 was approved by the local ethics committee of the NMRC for Oncology, Ministry of Health of the Russian Federation.

Development of the BC model

A skin fold was made on the side of the animal to create a subcutaneous tumor model, into which 0.3 ml of cell suspension was injected in RPMI-1640 nutrient medium.

Anesthesia was administered in two-stages to create an orthotopic model of animals: premedication with xylazine (20 mg/kg) and anesthesia with zoletil (50 mg/kg). Anesthetized animals were injected into the fatty tissue of the mammary gland with a suspension of tumor cells in a volume of 0.2 ml in a nutrient medium RPMI-1640. Each animal was injected with 3*107 cells.

Tumor growth was observed for 28 days from the moment of injection and measurements of tumor nodes were carried out 2 times a week until the end of the experiment. The volume of tumor nodes was calculated by the formula:

$V = (L*W*H) / 6*\pi$, where

V is the volume of the tumor node; L is the length of the tumor node; W is the width of the tumor node; H is the height of the tumor node.

After 28 days, the animals were euthanized in a CO_2 chamber.

Statistical analysis of the results

The Microsoft 10 and Statistica 10 software packages were used to analyze the results. The Shapiro-Wilk criterion was used to check for the normality of the obtained data sample. The results were evaluated using median and percentiles. The nonparametric Mann-Whitney criterion was used to assess the reliability of the differences.

STUDY RESULTS AND THEIR DISCUSSION

In the course of this work, the dynamics of the growth of tumor nodes at different injection sites was determined. With subcutaneous injection, the most successful was the injection of tumor cells, a certified VT20 line. At the end of the experiment, the median of tumor nodes in this group was 100.32 [91.15; 113.99] mm^3. The growth of tumor nodes was noted in 5 animals in the group (83.33 %). In the group with subcutaneous injection of primary tumor cell culture on the 28th day of the experiment, the median of tumor nodes was 88.79 [86.60; 90.86] mm^3, which is 11.49 % less than in the group with the introduction of a certified culture. The formation of tumor nodes was observed in 5 animals (83.33 %). The lowest growth dynamics was observed in the group with a disaggregated tumor, where the median tumor node was 41.28 [32.96; 44.73] mm^3, which is 58 % less than in the group with a certified cell culture. Tumor nodes were observed in 4 animals in the group (66.67 %). Data on the growth dynamics of subcutaneous tumor nodes are shown in Figure 1.

During orthotopic injection of tumor material, it was revealed that in this growth variant, the median volume of tumor nodes in the group with certified VT20 cell culture and primary cell culture reached similar values – 149.22 [145.43; 153.58] and 148.25 [144.09; 149.81] mm^3. During this implantation, the growth of tumor nodes was observed in all 6 animals in the groups (100 %). In the group with the injection of a disaggregated tumor, the median volume of tumor nodes on the 28th day of the experiment was 73.24 [70.11; 78.19] mm^3, and the presence of tumor nodes was observed in 4 animals in the group (66.67 %). Data on the growth dynamics of orthotopic tumor nodes are presented in Figure 2.

A comparative analysis of the growth dynamics of tumor nodes in subcutaneous and orthotopic versions by injection of tumor cells revealed that both tumor lines and the resulting suspension of cells reached a significantly larger volume during orthotopic injection. The data on the comparative analysis of the growth of tumor nodes are presented in Figure 3.

According to the results obtained, it was revealed that orthotopic injection of tumor cells showed a significantly higher growth rate than subcutaneous injection. As well as analyzing various literature

data, we confirmed that orthotopic implantation is recommended for faster growth and achieving a larger volume of the tumor node [11, 12]. When assessing the growth characteristics of xenografts, an analysis of the growth of human cardioesophageal cancer in mouse models was carried out in one of the works of the NMRC for Oncology, Ministry of Health of Russia [12]. In the work of Kit S. O. et al. (2020), as well as in our work, a significant influence of the implantation site on the growth dynamics of the tumor node and the chance of xenograft engraftment was revealed, which is probably due to the influence of the environment surrounding the tumor node [12]. In the studies of Zibirov R. F. and Moserov S. A. (2018), Chen S. et al. (2023), it was shown that the tumor microenvironment through signaling molecules contributes to the successful engraftment of the tumor fragment, the growth of the tumor node, the initiation of neovasculation and the formation of metastases [13, 14]. This microenvironment is represented by a stroma with cells of various types, such cells include tumor-associated fibroblasts – in Zhang Ya's et al. study (2023), it was shown that these cells are activated by microenvironment factors such as TGF-β, monocytic chemotactic protein –1, fibroblast growth factor; they produce signaling proteins such as hepatocyte growth factor, insulin-like growth factor-1, stimulating the proliferation of tumor cells [15]. In addition, in the studies of Pastushenko E. with co-authors (2018) and Kuburich N. A. et al. (2023), the effect of tumor-associated fibroblasts on the induction of epithelial-mesenchymal transition (EMF) was demonstrated by the secretion of TGF-β, which activates genes encoding proteins necessary for mesenchymal cell functions (vimentin, N-cadherin, fibronectin-1) and suppressing the expression of proteins important for the epithelial phenotype (E-cadherin, cytokeratins and lamins) [16, 17]. The tumor microenvironment also includes T and B lymphocytes: in the work of Zibirov R. F. and Moserov S. A. (2018), a high content of interleukin-10 (IL-10), produced by tumor cells and contributing to the inhibition of cytotoxic activity of T lymphocytes, which contributes to the survival of tumor cells in the body, was revealed [13]. Data on the effect of B lymphocytes on tumor pathogenesis are ambiguous – in the work of Qin Yu. et al. (2021), it was shown that tumor infiltration by B lymphocytes is a positive prognostic marker. Such cells perform an antigen-presenting function and express CD80, CD86 molecules, activating CD4+ and CD8+ T cells [18]. However, in a study by Lindner S. et al.

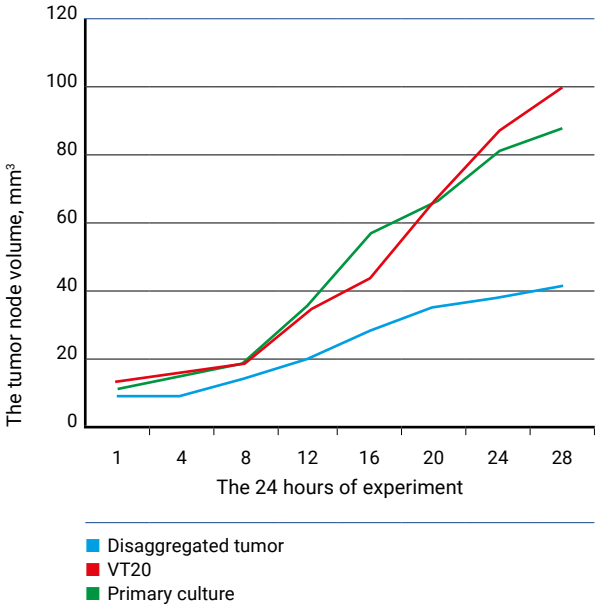

Fig. 1. Dynamics of growth of subcutaneous BC tumor nodes in the group with a disaggregated tumor, with injection of VT20, with injection of primary culture
Note: The data is presented as a median

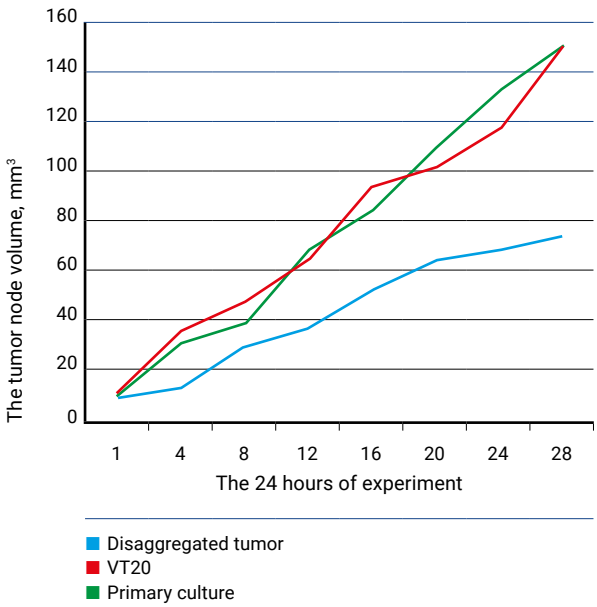

Fig. 2. Growth dynamics of orthotopic tumor nodes BC in the group with a disaggregated tumor, with injection of VT20, with injection of primary culture
Note: The data is presented as a median

(2013), it was shown that regulatory B cells secrete interleukin-10, interleukin-35, interleukin-6, TGF-β, contributing to the immunosuppression of the antitumor reaction [19]. Also, one of the main cells of the tumor microenvironment are mast cells that activate angiogenesis through histamine, heparin, the main fibroblast growth factor, vascular endothelial growth factor, TGF-β [13]. In the work of Liu S. et al. (2023), despite various contradictory data, the protumorogenic effect of mast cells in malignant formations of various diseases was shown [20]. Thus, orthotopic implantation of tumor cells into the body of an experimental animal contributes to the development of an appropriate microenvironment response, which, according to the analyzed literature and experimental data, contributes to more successful engraftment and growth of xenograft.

In our work, we also analyzed the effect of the type of transferred material on its survival and growth in the recipient's body. In the course of our work, we noted the most active growth and greater success of graft engraftment of the certified BT 20 cell line, however, the primary cell line formed in our institution also demonstrated a result close to the certified culture. The disaggregated tumor obtained from the patient had the lowest growth dynamics and the percentage of engraftment. Analyzing the literature data on the topic, we noted the need for intercellular communication for the development of physiological and pathological processes [21]. In laboratory practice, there are several ways to obtain a suspension of tumor cells: enzymatic, chemical and mechanical [22]. Proteolytic enzymes such as papain, trypsin, prote-

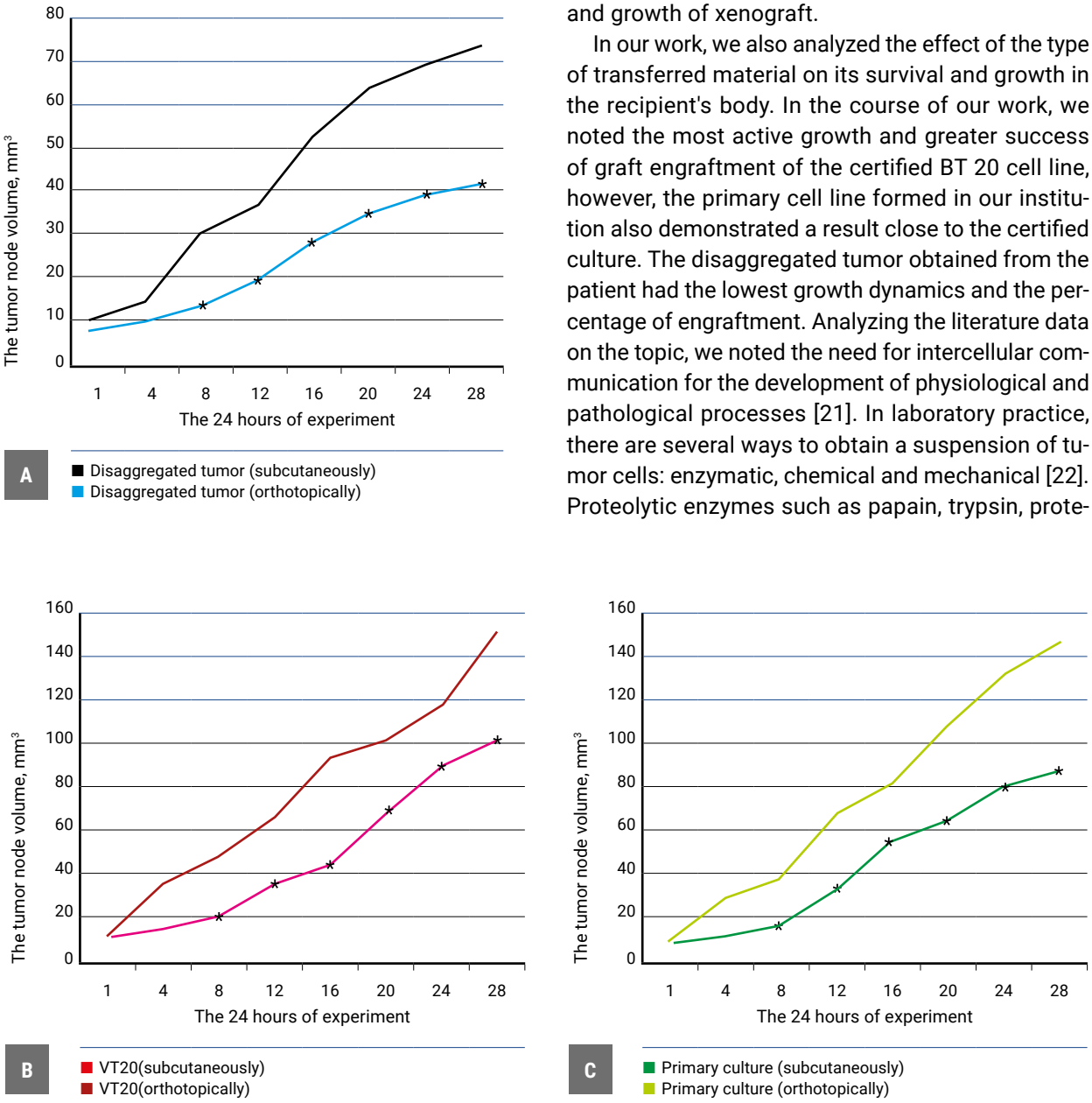

Fig. 3. Comparison of the growth dynamics between the groups of a disaggregated tumor, with VT20 injection, with primary culture injection with subcutaneous and orthotopic injection
Note: the data are presented as a median, * – statistically significant differences between the groups according to the Mann-Whitney criterion ($p < 0.05$)

ase, elastase and hyaluronidase are often used for enzymatic dissociation [23]. In a study by Janek K. et al. (2016), an enzymatic mixture was used to obtain a suspension of B C tumor cells, which included collagenase, a solution of dyspase and DNase [24]. However, according to a study by Nishikant T. and co-authors (2013), the most effective method of enzymatic dissociation against a breast tumor was the use of dispase II [25]. During chemical dissociation, it is necessary to achieve the leaching of calcium and magnesium cations from cells, in view of their important role in maintaining the integrity of the cell surface [26]. In a study by Damm G. et al. (2019), EDTA was used for chemical dissociation, which promotes the removal of Ca^{2+} and Mg^{2+} cations and leads to a decrease in intercellular interactions. Their work also describes the use of hypertonic solutions of sucrose, maltose and lactose to disrupt the gap contacts between cells [27]. Mechanical dissociation of tumor tissue is a simple and effective method of obtaining a cell suspension, consisting in crushing the resulting sample with scissors, homogenizing and filtering the resulting suspension [23]. Thus, in the work of Krbala L. et al. (2017), using a mechanical dissociation method, it was possible to form a primary cell line of human colorectal cancer obtained from a primary tumor with an efficiency of 39.4 %, and a cell line isolated from the corresponding metastases in the lymph nodes had an efficiency of up to 70 % [22]. However, many researchers believe that mechanical dissociation is more traumatic for cells than other methods and leads to significant cell death, which is not suitable for obtaining tumor cells [28–30].

Based on various literature data, it can be assumed that the use of enzymatic or chemical dissociation methods in our work with respect to the primary tumor could contribute to more successful engraftment of samples and greater growth dynamics of the obtained xenografts than with mechanical grinding of the sample. Determining an effective way to develop a human BC tumor model is necessary for us to conduct further studies of the nature of the course of this disease, as well as evaluate the effectiveness of new treatment methods.

CONCLUSION

In the course of the work, the growth dynamics of orthotopic and heterotopic in vivo models of breast cancer were evaluated. With orthotopic injection of tumor material, a higher percentage of engraftability was observed (66.67 %; 100 %). In addition, the primary BC line obtained in the course of this work had a growth dynamics of tumor nodes close to the certified culture, which gives grounds to use this line in further studies. In conclusion, it can be noted that we have developed an adequate BC tumor model for various methods of implantation of the material and with the possibility of further use in the study of mechanisms of carcinogenesis and testing of new pharmacological substances.

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Khodakova D. V. – search of literary sources;
Galina A. V. – analysis of the obtained experimental data;
Gurova S. V. – final conclusions;
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Shatova Yu. S. – scientific management.

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CLINICAL CASE REPORT

Metastatic lesions of the uterus, fallopian tubes and ovaries in undifferentiated pleomorphic sarcoma of the left tibia (clinical case)

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ABSTRACT

Undifferentiated pleomorphic osteosarcoma belongs to the group of rarely occurring tumors. Despite the treatment, the disease progresses in 30–40 % of patients with osteosarcomas. The main route of metastasis of bone tissue sarcomas is hematogenous, while lymphogenic spread is observed less frequently. As a rule, secondary metastatic changes occur in the lungs. Less often there is a secondary lesion of the bones of the skeleton and brain. Metastatic lesion of uterus, fallopian tubes and ovaries in malignant undifferentiated pleomorphic sarcoma is extremely rare. Therefore, we found it interesting to describe a clinical case of such a rare metastatic lesion. Patient K. underwent amputation of the left limb at the level of the lower third of the femur for undifferentiated pleomorphic sarcoma of the left tibia in 2019, and 4 courses of adjuvant polychemotherapy were performed. In 20 months after completion of complex treatment of the primary tumor, complaints of lower abdominal pain, increased body temperature up to 37.8 °C in the evenings appeared. According to the results of follow-up examination, a voluminous, multinodular, solid mass of merging character was detected in the pelvis, with total dimensions of up to 11 cm, and a cavitary mass of up to 5 cm was detected in the posterior vault. A trepan-biopsy of the mass in the projection of the right ovary was performed. The morphological picture in the volume of trepan biopsy specimens is characteristic of spindle cell sarcoma. Metastasis of undifferentiated pleomorphic bone sarcoma (malignant fibrous histiocytoma) is most likely. Due to metastatic lesions of the uterus, fallopian tubes, ovaries, omentum, mesentery and serous membrane of the colon loops, peritoneum of the bladder, surgical intervention in the volume of removal of the distal part of the sigmoid colon, rectosigmoid, upper ampullary parts of the rectum, uterus with fallopian tubes and ovaries, appendix was performed. Immunohistochemical study of the postoperative material revealed that the immunophenotype of tumor cells confirmed the morphological picture typical for undifferentiated pleomorphic bone sarcoma. The patient was further prescribed antitumor drug therapy. This clinical case demonstrates a rare, atypical metastasis of undifferentiated pleomorphic osteosarcoma, which allows to expand the knowledge about the flow of malignant diseases of this localization.

Keywords: undifferentiated pleomorphic sarcoma of bone, metastasis to the uterus, fallopian tubes and ovaries, surgical treatment of metastatic lesions, immunohistochemical analysis

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Compliance with ethical standards: the ethical principles presented by the World Medical Association Declaration of Helsinki, 1964, ed. 2013 were observed in the study. The study was approved by the ethics committee of the National Medical Research Centre for Oncology (extract from the protocol of the meeting No. 26 dated 09/11/2023. Informed consent was received from all participants of the study

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Conflict of interest: Kit O. I. has been the member of the editorial board of the South Russian Journal of Cancer since 2019, however he has no relation to the decision made upon publishing this article. The article has passed the review procedure accepted in the journal. The authors did not declare any other conflicts of interest

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3.1.6. Онкология, лучевая терапия

КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ

Метастатическое поражение матки, маточных труб и яичников при недифференцированной плеоморфной саркоме левой большеберцовой кости (клинический случай)

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РЕЗЮМЕ

Недифференцированная плеоморфная саркома костей относится к группе редко встречающихся опухолей. Несмотря на проводимое лечение, у 30–40 % пациентов с остеосаркомами заболевание прогрессирует. Основным путем метастазирования сарком костной ткани является гематогенный, реже наблюдается лимфогенное метастазирование. Как правило, вторичные метастатические изменения возникают в легких. Реже наблюдается вторичное поражение костей скелета, головного мозга. Метастатическое поражение матки, маточных труб и яичников при злокачественной недифференцированной плеоморфной саркоме является крайне редким. В связи с чем нам представилось интересным описать клинический случай такого редкого метастатического поражения. У пациентки К. по поводу недифференцированной плеоморфной саркомы левой большеберцовой кости в 2019 г. выполнена ампутация левой конечности на уровне нижней трети бедра, проведено 4 курса адъювантной полихимиотерапии. Через 20 месяцев после завершения комплексного лечения первичной опухоли появились жалобы на боли внизу живота, повышение температуры тела до 37,8 °С в вечернее время. По результатам дообследования в малом тазу выявлено объемное, многоузловое, солидное образование сливного характера, общими размерами до 11 см, в заднем своде выявлено полостное образование до 5 см. Выполнена трепан-биопсия образования в проекции правого яичника. Морфологическая картина в объеме трепан-биоптатов характерна для саркомы веретеноклеточного строения. Наиболее вероятен метастаз недифференцированной плеоморфной саркомы кости (злокачественной фиброзной гистиоцитомы). В связи с метастатическим поражением матки, маточных труб, яичников, большого сальника, брыжейки и серозной оболочки петель толстой кишки, брюшины мочевого пузыря выполнено хирургическое вмешательство в объеме удаления дистального отдела сигмовидной кишки, ректосигмоидного, верхне-ампулярного отделов прямой кишки, матки с маточными трубами и яичниками, аппендиксом. При проведении иммуногистохимического исследования послеоперационного материала выявлено, что иммунофенотип опухолевых клеток подтверждает морфологическую картину, характерную для недифференцированной плеоморфной саркомы кости. Далее пациентке назначена противоопухолевая лекарственная терапия. Данный клинический случай демонстрирует редкое, нетипичное метастазирование недифференцированной плеоморфной саркомы кости, что позволяет расширить знания о течении злокачественных заболеваний этой локализации.

Ключевые слова: недифференцированная плеоморфная саркома костей, метастазирование в матку, маточные трубы и яичники, хирургическое лечение метастатического поражения, иммуногистохимический анализ

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INTRODUCTION

In 1964, malignant fibrous histiocytoma was first described as an independent nosological form by J. O'Brien and A. Stout [1]. According to the World Health Organization's classification of soft tissue and bone tumors from 2020, the term "malignant fibrous bone histiocytoma" has been changed to "undifferentiated pleomorphic bone sarcoma" [2]. Undifferentiated pleomorphic bone sarcoma belongs to a group of rare tumors. The frequency ranges from 0.2–1 % of the number of all malignant neoplasms. As a rule, bone sarcomas are diagnosed before the age of 35 [3]. According to E. K. Laryukova et al. (2018), in more than 70 % of cases, the long tubular bones of the lower extremities are affected, mainly those parts of them that form the knee joint [4].

Even despite the treatment, 30–40 % of patients with osteosarcomas experience disease progression, while more than 80 % of them show metastases in the lungs [5]. Usually, bone sarcomas metastasize hematogenically (up to 90 % of cases), lymphogenic metastasis is less common. Hematogenous metastasis usually affects the lungs, less often the bones of the skeleton, the brain [6]. In patients with bone sarcomas, isolated metastatic lung damage occurs in approximately 40 % of cases [7].

Osteosarcoma metastasis to the lymph nodes is quite rare, the frequency of metastases to the lymph nodes ranges from 4 to 11 % [8]. In clinical practice, both single and multiple lymph nodes are affected by metastases [9]. In addition to the lesion of regional lymph nodes, distant lymph nodes may also be involved. The literature describes metastases of osteosarcoma of the femur in the lymph nodes of the lung root [10]. We did not find data on metastatic lesions of the uterus, fallopian tubes and ovaries in undifferentiated pleomorphic bone sarcoma among the analyzed literature sources.

We found it interesting to describe a rare case of metastasis of an undifferentiated pleomorphic sarcoma of the left tibia into the uterus, fallopian tubes and ovaries, with damage to the large omentum, mesentery and serous membrane of the loops of the colon, peritoneum of the bladder.

The purpose of the study: reports of such rare cases of metastatic lesions allow us to expand knowledge about the course of malignant neoplasms, to form an optimal treatment strategy for the patient in atypical clinical situations.

In 2005, at the age of 17, patient K. noticed an increase in the volume of the left shin, after an examination, a clinical diagnosis of fibrous dysplasia of the bones of the left shin was established. Segmental resection of the fibula on the left was performed in the pediatric orthopedic department in Krasnodar, and a histological conclusion was obtained – fibrous dysplasia. In 2006, she was operated at the H. I. Turner National Medical Research Center for Children's Orthopedics and Trauma Surgery of the Ministry of Health of the Russian Federation (Moscow St. Petersburg), resection of the focus of fibrous dysplasia of the left tibia was performed within healthy tissues, morphological conclusion – fibrous dysplasia.

Upon obtaining the anamnesis data, it was established that the patient's mother during pregnancy in 1987 lived in an area located within a radius of less than 400 kilometers from the Chernobyl nuclear power station.

In 2018, when the patient was 30 years old, there were complaints of an increase in the volume of the

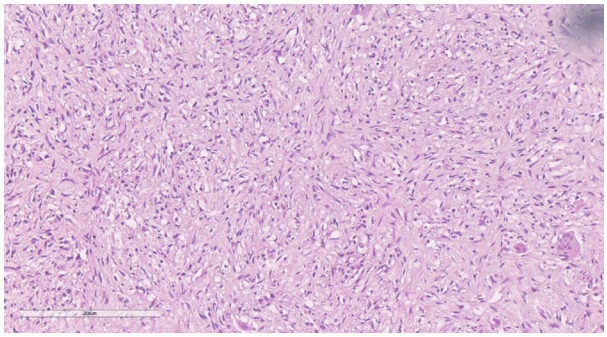

Fig. 1. Trepan biopsy – the picture is typical for spindle cell sarcoma (magnification × 200)

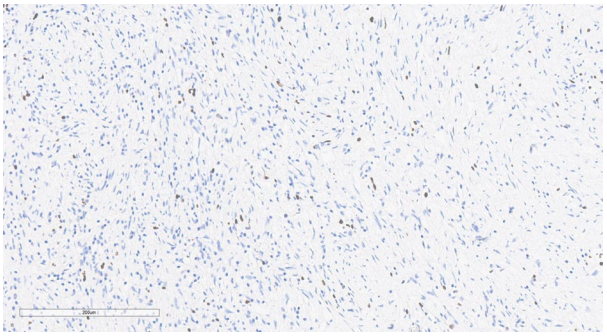

Fig. 2. IHC study, 2019 (the marker of proliferative activity Ki67 is positive in 30 % of tumor cell nuclei)

left shin and pain in this area. As is known, the main symptoms of primary undifferentiated pleomorphic bone sarcoma are pain and clinically detectable tumor formation. Almost half of the patients have these symptoms at the same time [11]. In December 2018, a follow-up examination was conducted at the medical center of the city of Krasnodar, which revealed a pathological focus in the left tibia, a biopsy was performed, a morphological conclusion was obtained fibrous bone dysplasia, no special treatment was carried out. In August 2019, the patient independently applied to the National Medical Research Centre for Oncology of the Russian Federation in Rostov-on-Don. A trepan biopsy of the pathological focus of the left tibia was performed, a histological conclusion was obtained – a morphological picture of spindle cell sarcoma, differentiated with fibrosarcoma, undifferentiated pleomorphic bone sarcoma (malignant fibrous histiocytoma). To determine the immunophenotype of tumor cells, an immunohistochemical study is recommended (Fig. 1).

The conclusion was obtained according to immunohistochemical analysis, the morphological picture and immunophenotype of tumor cells are most characteristic of undifferentiated pleomorphic bone sarcoma (Vimentin +, CD68+, Ki-67 30 %) (Fig. 2).

In September 2019, at the age of 31, the patient underwent amputation of the left lower limb at the level of the lower third of the thigh, the histological conclusion was an undifferentiated pleomorphic sarcoma (malignant fibrous bone histiocytoma). In the adjuvant mode, 2 courses of antitumor drug therapy were performed according to the HD AI scheme (doxorubicin 25 mg/m^2/day intravenously on days 1–3 (72-hour continuous infusion) + ifosfamide 2500 mg/m^2 (+ mesna 100 % of the dose of ifosfamide) intravenously on days 1–4 + granulocyte colony stimulating factor 5 mcg/kg subcutaneously on days 5–15) and 2 courses of antitumor drug therapy according to the HD I scheme (ifosfamide 2000 mg/m^2 intravenously on days 1–7 (+ mesna) + granulocyte colony stimulating factor 5 mcg/kg subcutaneously on days 8–16, every 3 weeks).

Further, the patient was observed by an oncologist at the place of residence, no signs of progression were detected. Thus, according to computed tomography of the chest, abdominal cavity and pelvic organs from 02/03/2021, no pathological changes were detected. In August 2021, the patient had a new coronavirus infection, after which there were complaints of pain in the lower abdomen, an increase in body temperature to 37.8 °C in the evening. In September 2021, the patient applied to the National Medical Research Centre for Oncology, examined by an oncogynecologist. During gynecological examination: the external genitalia are formed correctly, in the mirrors the cervix is without pathological changes, pushed back to the womb. During vaginal examination, the uterus is of normal size, pushed forward, in the posterior vault and above the body of the uterus, a solid volumetric formation is palpated, doubtfully mobile, the arches are free. Computed tomography of the chest organs, magnetic resonance imaging of the abdominal cavity and pelvic organs, ultrasound examination of the pelvic organs were performed. According to the results of the examination, a voluminous, multi-nodular, solid formation, of a draining nature, with total dimensions up to 11 cm, with uneven contours, in the posterior vault and close to the main substrate, a cavity, liquid formation up to 5 cm, with wall-mounted, hyperechogenic, intracavitary structures, in the form of "papillae", in the iliac region on the left mesenterically and close to the omentum, there are hypoechoic nodes up to 11–18 mm. No data were found for secondary changes in other organs.

Computed tomography of the chest organs was performed, which did not reveal any pathological

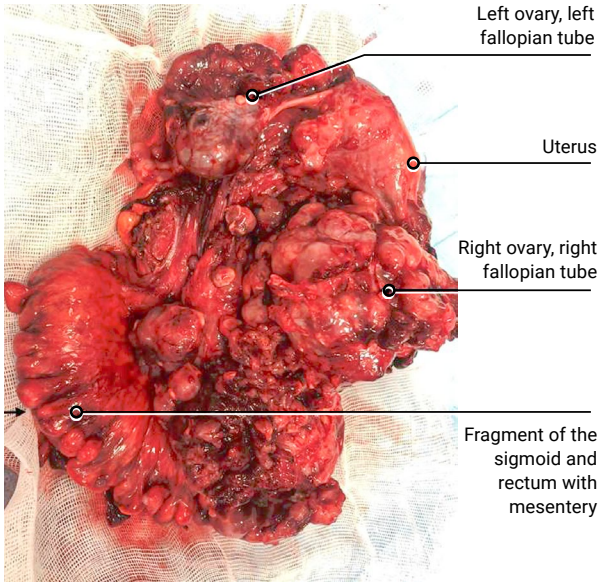

Fig. 3. Macro specimen view

changes in the lungs, lymph nodes and bone structures of the examined area.

Computed tomography of the left femur revealed a stable picture of the condition after amputation of the lower third of the left thigh, no signs of continued growth were revealed.

The level of cancer markers was determined, Ca-125 increased to 175.8 units/ml, Ne-4 increased to 74.08 pmol/l, ROMA index = 19.3 %.

A trepan biopsy of the formation in the projection of the right ovary was performed. The morphological picture in the volume of trepan biopsies is characteristic of spindle cell sarcoma. The most likely metastasis is undifferentiated pleomorphic bone sarcoma (malignant fibrous histiocytoma).

Taking into account the metastatic lesion of the pelvic organs, the absence of other distant metastases, a consultation of doctors of the National Medical Research Centre for Oncology decided on surgical treatment in the amount of removal of a pelvic tumor.

09/30/2021: in the supine position of the patient, a lower-median laparotomy was performed, minor ascites was observed during the revision of the abdominal cavity and pelvis, about 500 ml of straw-yellow effusion was evacuated. A tumor conglomerate lies in the wound, including a metastatically altered large omentum, a uterus with a tumor-like transformed right ovary, loops of the colon with multiple metastatic nodes along the serous membrane and mesentery, and the peritoneum of the bladder. The capsule of the liver is smooth, the peritoneum of the subdiaphragmatic space, the parietal and visceral peritoneum of the abdominal cavity are smooth, without metastatic lesion. Retroperitoneal lymph nodes are not enlarged. It was decided to remove the tumor conglomerate in a single block, for which it was necessary to perform anterior rectal resection with preventive ileostomy, pangisterectomy, appendectomy, extirpation of the large omentum. The distal sigmoid colon, rectosigmoid, upper ampullary rectum, uterus with fallopian tubes and ovaries, appendix was mobilized and removed as a single unit. Peritonectomy of the anterior arch was performed. A loop ileostomy has been formed in the right iliac region, at 30 cm from the dome of the cecum. Description of the macro specimen: as a single block, the body of the uterus is 5 × 5 × 4 cm, the cervix is 4 × 4 × 3 cm, a fragment of the sigmoid and rectum with mesentery, a large omentum, peritoneum of the bladder, appendix, metastatic nodes. Uterus with metastatic nodes along the serous membrane along the anterior and posterior surfaces, along the mesentery and serous lining of the intestine, multiple dense metastatic nodes from 1 to 3 cm in diameter, the left ovary is 4 × 3 cm with small cysts, the peritoneum of the bladder is totally affected by a metastatic process from 0.5 to 1 cm in diameter, the right ovary is totally replaced a tumorous tuberous tissue about 15 cm in diameter with cluster-like tumor growths along the outer capsule. A large omentum with multiple dense metastatic nodules, on an incision of a macroscopically sarcomatous nature (a type of "fish meat") (Fig. 3).

Postoperative histological analysis – in the tissues in the projection of the uterine appendages on the right and left, on the serous membrane of the uterus, in the mesentery of the colon, the growth of tumor tissue with foci of necrosis, represented by intertwining bundles of atypical fibroblast-like and epithelioid cells, with moderate nuclear polymorphism, mitosis

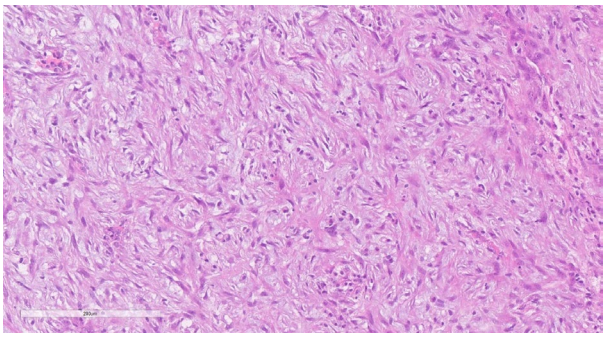

Fig. 4. Postoperative material – undifferentiated sarcoma (magnification × 200)

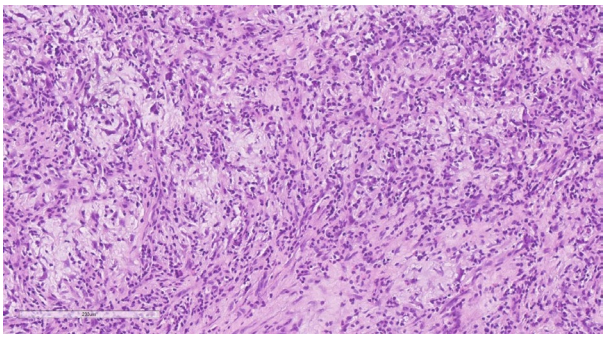

Fig. 5. Postoperative material presented with undifferentiated sarcoma with inflammatory infiltration (magnification × 200)

figures, with sections of myxoid stroma, with pronounced inflammatory (lymphocytic, granulocytic eosinophilic (and neutrophilic) infiltration, with lymphovascular invasion. Conclusion: the morphological picture is characteristic of undifferentiated sarcoma with growth into the uterine appendages and serous lining of the uterus, mesentery of the colon, appendix and omentum tissue, lymphovascular invasion. No tumor growth was detected in the resection lines of the vagina, colon and appendix (Fig. 4, 5).

During immunohistochemical examination, the immunophenotype of tumor cells confirms the morphological picture characteristic of undifferentiated pleomorphic bone sarcoma (Vimentin+, SMA+/-, CD68+/-) (Fig. 6).

The next stage of treatment was antitumor drug therapy.

DISCUSSION

The patient's first signs of bone pathology were revealed at the age of 17, when fibrotic dysplasia of the bones of the left shin was diagnosed. The causes of fibrotic dysplasia are currently not clear enough. The disease is based on a tumor-like process associated with the abnormal development of osteogenic mesenchyma. As a rule, fibrous dysplasia prevails in females aged 15–19 years [12].

Anamnestic data on the place of residence of the patient's mother during pregnancy in the territory located from the Chernobyl nuclear power plant within a radius of less than 400 kilometers were interesting. As is known, on April 26, 1986, as a result of the destruction of the reactor of the fourth power unit, a significant amount of radioactive substances was released into the environment. There is no doubt about the high radiosensitivity of the fetus at all stages of its development. We do not know for sure whether the radiation background had an effect on the patient's mother. However, it has been proven that intrauterine exposure to ionizing radiation can cause severe pathological consequences for the fetus. Among these consequences can be both gross violations of somatic development, as well as a decrease in intelligence, mental retardation [13].

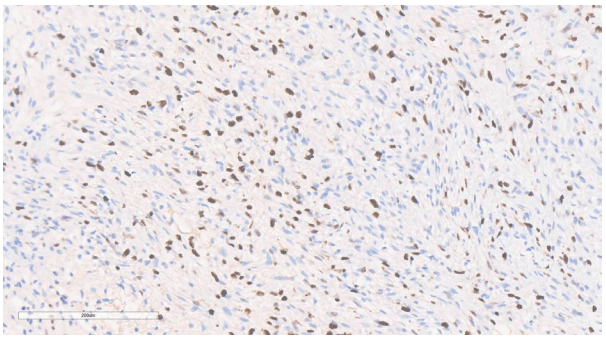

Fig. 6. IHC study, 2021 (marker of proliferative activity of Ki-67 in 60 % of tumor cell nuclei)

The case is interesting for the extremely rare localization of metastasis of undifferentiated pleomorphic bone sarcoma. It is known that more than 80 % of patients with bone sarcomas have lung metastases. According to the clinical recommendations of the Ministry of Health of the Russian Federation, in the treatment of metastatic forms of osteosarcoma, it is recommended to perform surgical treatment in combination with chemotherapy if possible [14]. According to the literature, in isolated metastatic lung damage, complete surgical removal of these metastases can ensure a 40 % 5-year survival rate [3]. The metastasis of malignant undifferentiated pleomorphic bone sarcoma into the uterus, fallopian tubes and ovaries has not been described in the available literature.

CONCLUSION

Following the completion of complex treatment of undifferentiated pleomorphic sarcoma of the left tibia, the progression of the disease with a rare localization of metastatic lesions of the uterus, fallopian tubes and ovaries was revealed in the patient in the given clinical case. Despite the spread of the tumor in the pelvis, secondary changes in the lungs were not detected. Due to the absence of other metastatic foci, it became possible to perform radical surgical intervention. Analyzing the above, it can be assumed that the complete surgical removal of metastatic focuses in combination with ongoing antitumor drug therapy will improve the prognosis of the disease. Currently, the period from the moment of initial diagnosis of undifferentiated pleomorphic sarcoma of the left tibia is 43 months.

Reports of such rare cases of metastatic lesions allow us to expand knowledge about the course of malignant neoplasms, to form an optimal treatment strategy for the patient in atypical clinical situations.

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Vladimirova L. Yu. – study concept and design, scientific editing;
Kalabanova E. A. – collection, analysis and interpretation of data, manuscript writing, material processing, preparation of references, preparation of the article;
Lapteva T. O. – morphological and immunological tests, preparation of figures according to morphological and immunological tests;
Barashev A. A. – surgical treatment;
Eremin K. S. – morphological and immunological tests;
Ardzha A. Yu. – technical editing, preparation of references.

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CLINICAL CASE REPORT

Characteristics of anesthetic and surgical tactics in treatment of a patient with a giant thyroid mass in a cancer center (clinical case)

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ABSTRACT

This paper describes an example of radical surgical treatment of a patient with a giant retrosternal goiter complicated by compression of the organs of the neck and mediastinum. Considering all the risks and possible complications, we should take into account the fact that enlarged thyroid (T) body with retrosternal location can cause displacement and stenosis of the trachea and esophagus, and dislocation of large vessels and nerves of the mediastinum. This anatomical specificity is an imminent threat to successful treatment, and it also carries a certain risk of asphyxia and sudden death of the patient. In this clinical case, radical surgical treatment in this patient included sequential mobilization in two pleural cavities, and then the total removal of T through the traditional surgical access. The anesthetic complexity to support the surgical intervention involved both difficult intubation due to tracheal stenosis, and also the required separate ventilation of the lungs to visualize anatomical structures and mobilize a multinodular formation in two pleural cavities. Standard methods of artificial lung ventilation could be ineffective and even dangerous in this case due to the location and size of the tumor. We focused our attention on high-frequency ventilation (HFV), the best method of respiratory support during surgeries for tracheal and bronchial pathologies. The main task of the anesthetic team in this clinical case was to prevent the development of hypercapnia and hypoxia during intubation of the stenotic tracheal segment, and then adequate ventilation of the lungs with reduced area of proper gas exchange due to bilateral surgical pneumothorax. Thus, the full treatment was carried out due to the only safe method of compensating lung ventilation with anesthesia by HFV. The applied HFV method creates an adequate gas exchange in the lungs due to the small ventilation volume and high frequency of respiratory cycles per minute. HFV both prevented the development of threatening complications during intubation of the stenotic tracheal area and ensured an adequate gas exchange during successive thoracoscopic stages of thyroid tumor mobilization.

Keywords: thyroid, multinodular goiter, compression of organs of the neck and mediastinum, thyroidectomy, artificial lung ventilation

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Compliance with ethical standards: the ethical principles presented by the World Medical Association Declaration of Helsinki, 1964, ed. 2013 were observed in the study. The study was approved by the ethics committee of the National Medical Research Centre for Oncology (extract from the protocol of the meeting No. 19 dated 22/11/2021). Informed consent was received from all participants of the study

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Conflict of interest: the authors declare that there are no obvious and potential conflicts of interest associated with the publication of this article

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3.1.6. Онкология, лучевая терапия
КЛИНИЧЕСКИЙ СЛУЧАЙ

Особенности анестезиологической и хирургической тактики лечения больного с гигантским объемным образованием щитовидной железы в условиях онкологического центра (клинический случай)

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РЕЗЮМЕ

Описан клинический пример радикального хирургического лечения пациента с гигантским ретростернальным зобом, осложненным компрессией органов шеи и средостения. Рассматривая все риски и возможные осложнения, следует учитывать тот факт, что увеличенная щитовидная железа (ЩЖ) с ретростернальной локализацией может вызывать смещение и стеноз трахеи и пищевода, дислокацию крупных сосудов и нервов средостения. Эта анатомическая специфика является не только неминуемой угрозой успешного лечения, но и несет определенный риск развития асфиксии и внезапной смерти пациента. В нашем клиническом случае радикальное хирургическое лечение у данного пациента предусматривало последовательную мобилизацию в двух плевральных полостях, а затем тотальное удаление ЩЖ из традиционного хирургического доступа. При этом сложность анестезиологического обеспечения хирургического вмешательства представляла не только трудная интубация, обусловленная стенозом трахеи, но и необходимая реализация раздельной вентиляции легких для возможности визуализации анатомических структур и мобилизации многоузлового образования в двух плевральных полостях. Стандартные методики искусственной вентиляции легких из-за особенностей локализации и размеров опухоли в данном случае могли быть малоэффективны и опасны. Наше внимание было направлено на применение метода респираторного обеспечения во время операции – высокочастотной искусственной вентиляции легких (ВЧ ИВЛ), которая занимает лидирующие позиции в обеспечении хирургического лечения патологии трахеи и бронхов. Следует отметить, что в данном клиническом случае основной задачей анестезиологической бригады было предупреждение развития гиперкапнии и гипоксии при интубации стенозирующего сегмента трахеи, а затем адекватная вентиляция легких при снижении площади должного газообмена вследствие двустороннего операционного пневмоторакса. Таким образом, проведение полноценного лечения состоялось благодаря единственно безопасному способу заместительной вентиляции легких во время анестезии методом ВЧ ИВЛ. Применяемый метод ИВЛ создает адекватный газообмен в легких за счет малого вентиляционного объема и высокой частоты дыхательных циклов в минуту. Применение ВЧ ИВЛ позволило не только избежать развития угрожающих осложнений во время интубации стенозирующего участка трахеи, но и обеспечило адекватный газообмен во время последовательных торакоскопических этапов мобилизации опухоли щитовидной железы.

Ключевые слова: щитовидная железа, многоузловой зоб, компрессия органов шеи и средостения, тиреоидэктомия, искусственная вентиляция легких

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Конфликт интересов: все авторы заявляют об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи

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INTRODUCTION

To date, international and Russian clinical guidelines have been developed for the diagnosis and treatment of thyroid diseases. But as before, patients with giant goiter and manifestations of compression syndrome usually seek medical help in an emergency [1]. The main clinical symptoms of compression of the neck and mediastinal organs are: pathological breathing with obstruction on the inhalation or exhalation in 73.5 % of cases, varying degrees of esophageal dysphagia (8.7 % of cases), superior vena cava syndrome (3.2 % of cases), and in 1 % of patients chronic hypoxia provoked the development of cardiovascular and cerebral insufficiency [2].

Nontoxic multinodular goiter (E04.2) is a clinical concept that includes all detectable focal thyroid formations, which are characterized by various morphological features. On average, according to statistics in the Russian Federation, the incidence of nodular goiter is 31 % [3]. In 20 % of cases, goiter has a cervical-thoracic localization, of which 80 % of cases are diagnosed in the anterior mediastinum. The peculiarity of this tumor topography is the delayed growth, late diagnosis and complicated course of the disease [4]. According to the diagnostic criteria of the Bethesda classification (2016), with a diffuse increase in both lobes of the thyroid gland, as well as with suspected malignant tumor, surgical intervention in the volume of hemithyroidectomy or thyroidectomy is necessary [2, 5]. It should be noted that the proportion of thyroid cancer in relation to benign nodules ranges from 2 to 30 %, according to various data. The prognosis of the disease largely depends on early diagnosis, which, in some cases, is out of time and is due to prolonged tumor growth against the background of other thyroid diseases [6].

Considering all the risks and possible complications, one should take into account the fact that an enlarged thyroid gland with retrosternal localization can cause displacement and stenosis of the trachea and esophagus, as well as dislocation of large vessels and nerves of the mediastinum. This anatomical specificity is not only an imminent threat to successful treatment, but also carries a certain risk of asphyxia and sudden death of the patient [7].

To carry out adequate and safe anesthesia during radical surgical removal of a giant thyroid neoplasm, the anesthesiologist must provide for all complications of the intra- and early postoperative period, with the possibility of emergency measures to restore the patency of the upper respiratory tract. The degree of tracheal stenosis according to the Cotton-Mayer classification serves as a determining factor in choosing the tactics of intubation and ensuring adequate ventilation during surgery. Thus, at grade I, when tracheal obstruction is less than 50 %, standard patient management is possible, and at grade II, obstruction is from 51 % to 70 %, at grade III 71–90 % stenosis and grade IV complete stenosis, anesthesia tactics using endoscopic methods should be individually determined [8].

In fact, acute violation of the patency of the respiratory tract in chest goiter with compression syndrome and tracheal stenosis can occur at any stage of anesthesiological support, during induction of anesthesia or intubation of the trachea, as well as during mobilization and removal of tumor formation [7]. For adequate visualization of the mediastinal organs and mobilization of the thyroid gland in the pleural cavities, it is necessary to ensure lung collapse on the side of the operation. This is done through the technical reception of general anesthesia using single-lung ventilation [9]. At the same time, tracheal intubation should be performed with a two-light endotracheal tube for separate ventilation of the lungs. The complexity of this manipulation, even in typical conditions, is not always safe for patients, and in some cases cannot be performed at all [10]. The giant thyroid gland aggravates the situation, located in the mediastinum, it leads to significant changes in the anatomy of the trachea and bronchi, displacement and compression of their lumen, which undoubtedly complicates the separation of the lungs for ventilation. In our patient, intubation with a double-light tube was immediately excluded. The presence of tracheal stenosis of more than 70 % does not allow for unhindered intubation of the patient, even with a single-light endotracheal tube, much smaller in diameter. Thus, the only safe method of replacement ventilation during anesthesia in this patient was the use of high-frequency ventilation. The main value of the method used is to ensure adequate gas exchange in the lungs due to the small ventilation volume and high frequency of respiratory cycles per minute. At the same time, the diameter of the adapted catheter, which is used instead of an intubation tube, is much smaller than the size

of the stenosing section of the trachea. Prolonged compression of the trachea caused by enlarged thyroid gland leads to degenerative cartilage atrophy and tracheomalacia, as it was observed in our patient [11]. And at this point, of particular importance is the fact that for high-frequency (HF) artificial lung ventilation (ventilator), a thin and elastic adapted catheter is used, which does not create additional pressure on the trachea. It follows from the above that the absence of a traumatic factor will avoid additional damage and rupture of the trachea, which already has an initially altered architectonics of blood supply and deformation of the fibrous ring. In addition, the preservation of the integrity of the tracheal tissue, under these conditions of lung ventilation, will prevent the development of a detrimental complication, which is mediastinitis. The total spread of the inflammatory process in the mediastinum and, as a result, the progression of the systemic inflammatory reaction of the body, will inevitably lead to adverse treatment results and fatal consequences for the patient.

The purpose of the study was to demonstrate by this clinical case the possibility of safe and adequate provision of ventilation by HF ventilation to a patient with a giant retrosternal goiter complicated by compression of the neck and mediastinal organs during a single-stage operation consisting of three stages of mobilization, in the right and then in the left pleural cavity, followed by total removal of the thyroid gland from the median cervical access.

Clinical case

64 years old patient M, was admitted to the Department of Head and Neck tumors of National Medical Research Centre for Oncology in November 2022 with complaints about difficulty breathing with minimal physical exertion and during sleep, persistent cough, difficulty passing solid food through the esophagus, facial swelling. He considers himself ill since October 2022, when the above-mentioned complaints appeared. The patient was further examined and diagnosed with a thyroid tumor with a retrosternal spread.

Findings during physical examination revealed: height 176 cm, weight 94 kg, body mass index is 30.35 kg/m^2. The patient's condition is satisfactory. Patient is conscious. The skin is of normal color, the body complexity is normosthenical, the nutrition is satisfactory. There are no peripheral edema, soft tissue turgor is reduced. The temperature is within the normal range. Blood pressure indicators on both brachial arteries are 150/90 mmHg, heart rate is 96 per minute, pulse of satisfactory tension filling, there is no pulse deficit. Auscultation reveals: shortness of breath of a mixed nature, respiratory rate 20–22 per minute, vesicular breathing, no wheezing, rhythmic muffled heart tones. There were no pathological changes on the behalf of other organs. Significant comorbidity, in addition to hypertension, was not detected (therapy with beta-blockers and antiaggregant drugs). According to the patient, he did not take thyrostatic therapy. Examination: the neck is deformed due to tumor formation of the thyroid gland with a retrosternal spread (II degree according to WHO), the thyroid gland is painless, soft, non-mobile, there is swelling of subcutaneous fat in the supraclavicular areas on both sides.

According to ultrasound of the thyroid gland, it was revealed: the volume of the right lobe is 60.5 cm^3, the left lobe is 44 cm^3, the total volume is 104.5 cm^3; the parenchyma has solid multiple isoechogenic nodules with hypoechoic contours and dimensions on the right are 15 × 10 × 15 mm, on the left – 31 × 19 × 28 mm, which corresponds to the EU TIRADS category 4 [12]; regional lymph nodes enlarged to 5–7 mm, pronounced vascularization, no hyperechoic inclusions. Ultrasound conclusion: thyromegaly, pronounced diffuse changes in the type of thyroiditis, diffuse nodular goiter EU TIRADS 4, nodular formations of both lobes of the thyroid gland with intracoracic distribution; lymphadenopathy of the parotid lymph nodes on the right, multiple thyroid nodes with intracoracic distribution, it is categorically impossible to exclude tumor genesis. To verify the process, a fine needle aspiration biopsy of the thyroid gland was performed. Cytological conclusion: the material was obtained from the site of the cell goiter of the left and right lobes, which corresponds to the II diagnostic category according to the Bethesda classification (2016) [5]. Computed tomography of the neck and thoracic cavity organs with intravenous bolus contrast, multiplanar and three-dimensional reconstruction of the neck revealed a significant increase in the thyroid gland with a spread to the mediastinum, a volumetric effect and compression of the trachea (lumen narrowed to 6 mm), hyperplasia of the lymph nodes of the neck (Fig. 1). According to fi-

broscopy data, it was revealed that, starting from the second cartilage, the trachea deviates to the right, its lumen spirally unevenly narrows (up to 6 mm) due to external pressure along the lateral and membranous walls to the level of tracheal bifurcation, the mucous membrane is hyperemic throughout.

A clinical diagnosis was made: a thyroid tumor with a retrosternal spread. Complication of the underlying disease: compression syndrome of the neck and mediastinal organs (compression of the trachea up to 6 mm). Concomitant diseases: hypertension stage 2, hypertension grade II, risk 4.

The council decided to perform radical surgical treatment in this patient with sequential mobilization in two pleural cavities, and then total removal of the thyroid gland from the traditional surgical access for this pathology. Anesthesiological support should be carried out using the method of high-frequency artificial lung ventilation (HFV).

On 01/16/2023, planned surgical intervention was performed in the following volume: video thoracoscopy on the right, video thoracoscopy on the left, mobilization of tumor formation, thyroidectomy. After premedication, patient M. was taken to the operating unit of National Medical Research Centre for Oncology for elective surgery. Initial functional data: blood pressure 146/96 mmHg, heart rate 104 per minute, respiratory rate (RR) 20 per minute, blood saturation 93 %. A puncture and catheterization of the cubital vein was performed. Intraoperative monitoring of the patient's functional state corresponded to the Harvard standard (cardiac monitoring, control of blood gas composition, assessment of the bispectral index and neuromuscular conduction). The operation started at 10:10am and ended at 3:50 pm. After preoxygenation with oxygen through a facial mask, induction of anesthesia with fentanyl 2.5 mg/kg, propofol at a dose of 3.0 mg/kg and rocuronium bromide 0.8 mg/kg was initiated. On the first attempt, under visual control (using the 840XDL video laryngoscope (Karl Storz – Endoscope, Germany) unhindered, an HF ventilator catheter was inserted into the trachea beyond the stenosis area. The HF ventilator mode is a jet catheter (artificial lung ventilation device high–frequency jet ventilator-HF/100 "ZisLine"). Also, an extraordinary situation was envisaged, which could arise if it was impossible to carry a ventilation catheter through the stenosing segment of the trachea due to mucosal edema or obstruction of the respiratory tract by sputum. In this case, it was envisaged to use an RF ventilator in injection mode. To do this, it was necessary to conduct a single-light endotracheal tube, using a video laryngoscope, behind the glottis, to the tracheal stenosis site and begin forced ventilation of the lungs. The injection mode also provides adequate ventilation, but, in our opinion, is less safe for this patient. This is explained by the three-fold change of the patient's position on the operating table during surgery (on the left side, on the right side and on the back). Displacement of the endotracheal intubation tube during the patient's movement, even if well fixed, has a high probability. The use of jet

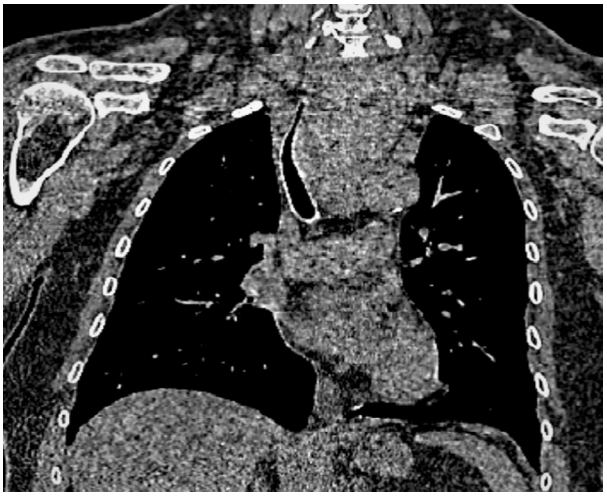

Fig. 1. Spiral X-ray computed tomography (SCT) of the neck and chest organs

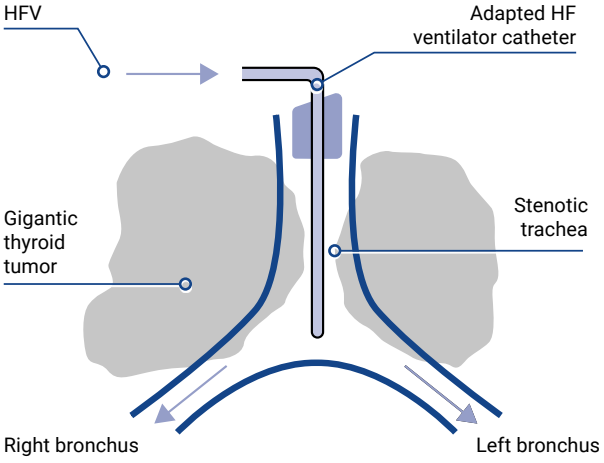

Fig. 2. The scheme of the HF ventilation

catheter ventilation completely eliminates the risk of dislocation of the adapted ventilation catheter. The mode of ventilation indicators at the time of the start of the operation was: minute ventilation frequency – 160 per minute, minute volume of ventilation (MV) – 11.5 l/min, tidal volume (Vt) – 140 ml. With HF ventilation, there is no possibility of spirometric determination of the required volume of minute ventilation or MV. Therefore, this parameter was calculated using the standard formula of T. M. Darbinyan:

MOD (l) = BM (kg) / 10 + 1,

where BM (kg) stands for body mass.

Determining the proper MV allows you to individually adjust the parameters of the HF ventilator in accordance with the respiratory needs of the patient and avoid the development of hypercapnia. The adequacy of ventilation and the replacement of respiratory function in full was confirmed by the data of the gas analyzer. The scheme of the HF ventilation is shown in figure 2.

The course of the operation. In the patient's position on the left side, a port and a video camera are inserted into the pleural cavity in the 7th intercostal space along the posterior axial line on the right. Under visual control, additional trocars were inserted through additional incisions in the 5th and 6th intercostal space along the anterior and posterior axillary lines and in the 7th intercostal space along the mid-axillary line. During the revision of the right pleural cavity, it was revealed that the thyroid gland is in the posterior mediastinum, the tumor shifts the esophagus and trachea to the right. The first stage of the operation was decided to mobilize the tumor. With the help of ultrasonic scissors, the parietal pleura was dissected with the mobilization of nodular formation from the trachea and esophagus. The lower edge of the tumor is located 0.5 cm above the anterior pulmonary trunk. Due to the inability to visualize the lower edge of the tumor with a surgical suturing device, v. Azygos was stitched and crossed, thorough hemostasis, drainage and layered suturing of the wound were performed. Then the patient was transposed to the right side. In the patient's position on the right side, a port was inserted into the pleural cavity in the 6th intercostal space along the antero-axillary line on the left, then a video camera was inserted and, under visual control, through additional incisions in the 5th and 6th intercostal space along the middle axillary and posterior axillary lines, as well as in the 9th intercostal space Additional trocars have been introduced along the rear-axillary line. The parietal pleura was opened in the posterior mediastinum above the aortic arch, and the tumor was mobilized from the left pleural cavity. The pleural cavity is sutured. Next, an arcuate incision of the neck skin was made 1 cm above the jugular sternum, the skin flaps were separated, the rectus muscles of the neck were dissected between the clamps. The revision revealed: the right lobe of the thyroid gland is enlarged, the gland tissue is totally replaced by a tumor of a tightly elastic consistency, the left lobe is large, the gland tissue is totally replaced by a multi-node tumor. The lower edge of the right lobe is located behind the sternum up to 8 cm away at the level of the tracheal bifurcation, closely adheres to the lower wall of the trachea. The right lobe of the thyroid gland was removed in blunt and acute ways, while the right recurrent laryngeal nerve was preserved. The left recurrent nerve was also visualized and isolated. Then the left lobe of the thyroid gland, the upper and lower vascular bundles are crossed and bandaged from 2 sides. Hemostasis, drainage, and layered suturing of the wound were performed. The operation was performed radically (Fig. 3, 4).

The parameters of the HF ventilator were changed depending on the stages of the operation, considering surgical manipulations in the right or left pleural cavities. At the time of surgical pneumothorax and in the absence of tightness of the pleural cavity, the minute ventilation frequency was increased to 200 per minute. Visually, the lung is partially collapsed, while the gas exchange area is preserved. According to pulse oximetry, blood oxygen saturation was 100 %. The presented frame of the video recording of the operation shows that the lung, reduced in size, does not interfere with the visualization and mobilization of thyroid tumor formation in the mediastinum (Fig. 5).

During the entire period of anesthesia, no cardiorespiratory disorders were recorded. At the end of the operation, with complete restoration of muscle tone and consciousness, as well as with adequate indicators of blood oxygen saturation, the ventilation catheter was removed unhindered. Postoperative monitoring of the gas composition of arterial blood revealed no serious violations: pCO_2 41.2 mmHg, pO2 120 mmHg, pH 7,250, BE 2.4 mmol/l, HCO_3 29.2 mmol/L, SO_2 97 %, Na+

139.0 mmol/L, K+ 3.9 mmol/L, SI – 101.0 mmol/l, Ca^{2+} ion – 2.01 mmol/l. On the 1st day after surgery, the patient's condition corresponded to the timing of postoperative treatment. With constant oxygen insufflation through a nasal catheter, the gas composition of arterial blood corresponded to normal values. On the 2nd day after the operation, the patient was transferred to the surgical department under the supervision of the attending physician. Postoperative therapy met the standards of medical care, which included antibiotic therapy, prevention of thrombogenic complications, and inhalation with mucolytics. Patient M. was discharged from the hospital on the 14th day, which corresponds to the standards of surgical treatment for uncomplicated thyroidectomy.

Description of the macro specimen: the right lobe of the thyroid gland, totally replaced by a multi-nodular tumor, of dense elastic consistency, nodes 2.5–3 cm in size; the left lobe of the thyroid gland is totally replaced by a multi-nodular tumor of dense consistency, nodes 2.5–7.5 cm in size (Fig. 6). Histological analysis No. 3778/23: morphological changes in the tissue of both lobes of the thyroid gland are distinctive for nodular follicular disease / multi-nodular goiter.

DISCUSSION

The incidence of thyroid tumor pathology in our country and the world remains high. In accordance with Russian clinical guidelines, radioactive iodine therapy or thyroidectomy are among the main methods of treating multi-node thyroid diseases [3]. Some patients seek medical help in an emergency, when, as a rule, clinical symptoms rapidly increase with decompensated compression of the tumor formation

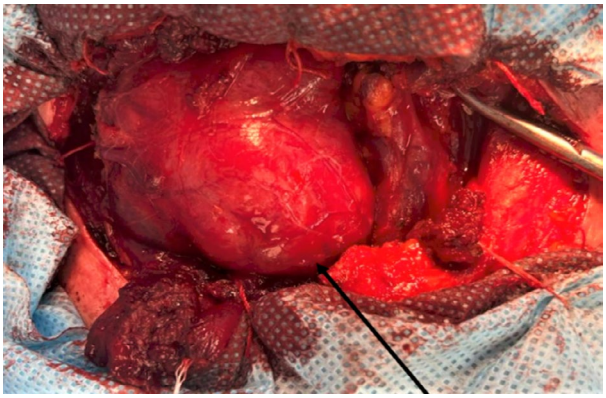

Fig. 3. The right lobe of the thyroid gland

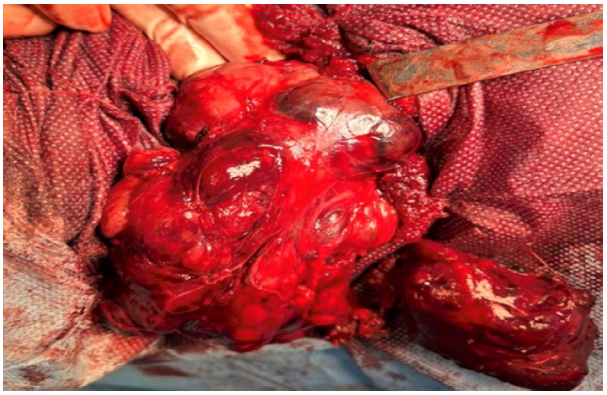

Fig. 4. The left lobe of the thyroid gland

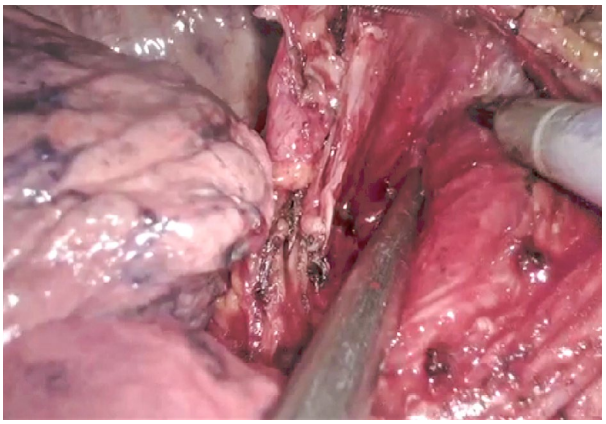

Fig. 5. Mobilization of the thyroid gland and partial lung collapse under conditions of HF V

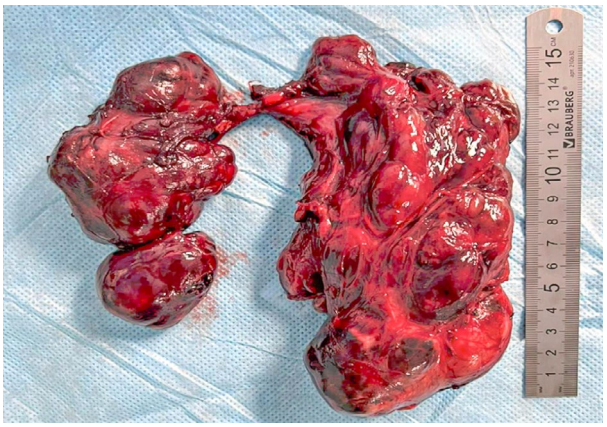

Fig. 6. Macro specimen: thyroid gland (two lobes with tumor nodes)

of the thyroid gland of the trachea, esophagus, vessels, and nerves of the mediastinum. Compression syndrome is one of the most difficult and unpredictable complications of nodular goiter. Mechanical compression of the trachea from the outside by a giant nodular formation of the thyroid gland is the cause of the development of respiratory failure of varying degrees of compensation. Preventing the development of asphyxia in a patient is the main indication for surgical treatment [1, 13].

The tactics of anesthesia with significant volume formation of the thyroid gland, and clinical signs of tracheal stenosis are determined by the risk of obviously difficult intubation. To overcome this factor, various technical possibilities are used: intubation using endoscopic equipment or the use of a videolaryngoscope. In our clinical case, the complexity of anesthesiological provision of radical surgical intervention was represented not only by difficult intubation due to tracheal stenosis, but also by the necessary implementation of separate ventilation of the lungs to enable visualization of anatomical structures and mobilization of a multi-node formation in two pleural cavities.

Standard methods of artificial lung ventilation, due to the peculiarities of the localization and size of the tumor in this case, could be ineffective and dangerous. Our attention was focused on the use of the respiratory support method during surgery – HF ventilation, which occupies a leading position in providing surgical treatment of pathology of the trachea and bronchi. The peculiarity of HF ventilation is the absence of the need to comply with the conditions of tightness – "respirator-patient", the technique is carried out on the principle of "open circuit". The high rate of respiratory cycles per minute guarantees the introduction of sufficient gas flow to create maximum respiratory support for the patient. In addition, according to a number of studies, a high level of oxygenating ability of the HF ventilator was noted in comparison with the standard ventilator. This is explained from the position of creating an increased partial pressure of oxygen in the composition of the alveolar gas, which is manifested by an increase in arterial oxygenation with preserved CO_2 elimination. Attention was also drawn to the fact that in conditions of jet HF ventilation in the ventilation-perfusion ratio, ventilation prevails over perfusion, unlike standard ventilation with a significant predominance of perfusion over ventilation, which contributes to increased oxygenation [9]. In this context, the use of HF ventilation is actively used in thoracic surgery not only for elective surgical interventions, but also in urgent situations such as lung abscess, massive pulmonary bleeding, and reconstructive operations for bronchopleural fistulas [14].

It should be noted that in this clinical case, the main task of the anesthesiological team was to prevent the development of hypercapnia and hypoxia during intubation of the stenosing segment of the trachea, and then adequate ventilation of the lungs with a decrease in proper gas exchange due to bilateral surgical pneumothorax. This was ensured by the effective use of the RF ventilator potential and made it possible to minimize tracheal injury and optimize functional gas exchange in our patient.

CONCLUSION

Based on the presented clinical data, it can be noted that the possibility of using modern technologies for anesthesiological ventilation in patients with giant thyroid tumors and compression syndrome makes it possible to carry out surgical treatment in full and avoid the development of life-threatening complications in patients. The presented clinical case demonstrated that this technique is not only effective and safe, but also the only correct one in a patient with a complicated course of retrosternal goiter. It should be noted that the success of the treatment completely depended on the professionalism of the staff of the cancer center, the well-coordinated work of the multidisciplinary team made it possible to provide specialized care and minimize complications and risks in this patient.

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REVIEW

Immunologic aspects of colorectal cancer progression

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ABSTRACT

Colorectal cancer remains in the leading positions in the structures of morbidity and mortality among both sexes. A large number of studies are aimed to reveal new biomarkers targeted at both early diagnosis and improving the effectiveness of drug therapy. Colorectal carcinoma (CC) is heterogeneous in its morphological, molecular and immunological aspects and is a heterogeneous disease. The existing molecular genetic classifications and biomarkers capable of predicting the effectiveness of therapy aren't optimal enough. New prognostic markers would make it possible to identify a subgroup of patients with a high risk of tumor recurrence, for whom enhanced monitoring and diagnostic monitoring should be established, as well as the selection of highly effective methods in the treatment of colorectal cancer. It has been established that some immune cells in the tumor microenvironment are able to stimulate the development of disease progression. Cytokines and chemokines in the tumor microenvironment stimulate the development of metastases, and their serum levels reflect the current inflammatory response in the tumor tissue. The identification and analysis of immune markers involved in the processes of metastasis and the mechanisms of progression remains an important task of modern medicine. The purpose of the study was to analyze modern ideas about the importance of the immunological microenvironment in the progression of colorectal cancer. The effect of molecular heterogeneity of the tumor on the development of metastases, as well as on resistance to ongoing antitumor therapy. The review reflects the immunological characteristics of CC, including in the context of molecular biological subtypes. It describes the involvement of cells of the immune system (lymphocytes, macrophages) and their products (cytokines, chemokines) in the progression of colorectal cancer, including in the processes of neoangiogenesis, as well as the relationship of the T- and B-cell composition of the tumor microenvironment on the course of the disease. The review also shows the immunogenomic stratification of CC, which can be used to predict the response to immunotherapy for colorectal cancer.

Keywords: colorectal cancer, molecular genetic subtypes, tumor-associated macrophages, cytokines, chemokines

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ОБЗОР

Иммунологические аспекты прогрессирования колоректального рака

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РЕЗЮМЕ

Колоректальный рак в структурах заболеваемости и смертности среди обоих полов по-прежнему остается на лидирующих позициях. Большое количество исследований нацелено на получение новых биомаркеров, направленных как на раннюю диагностику, так и на улучшение эффективности лекарственной терапии. Колоректальная карцинома неоднородна по своим морфологическим, молекулярным и иммунологическим аспектам и представляет собой гетерогенное заболевание. Существующие молекулярно-генетические классификации и биомаркеры, способные прогнозировать эффективность терапии, неоптимальны. Новые прогностические маркеры позволили бы идентифицировать подгруппу пациентов с высоким риском рецидива опухоли, за которыми должен быть установлен усиленный контроль и диагностическое наблюдение, а также подбор высокоэффективных методов терапии колоректального рака. Установлено, что некоторые иммунные клетки в микроокружении опухоли способны стимулировать развитие прогрессирования заболевания. Цитокины и хемокины в микроокружении опухоли стимулируют развитие метастазов, а их уровни в сыворотке крови отражают текущую воспалительную реакцию в опухолевой ткани. Выявление и анализ иммунных маркеров, участвующих в процессах метастазирования и механизмах прогрессирования, остается важной задачей современной медицины. Целью работы явился анализ современных представлений о значении иммунологического микроокружения, в прогрессировании колоректального рака. Влияние молекулярной гетерогенности опухоли на развитие метастазов, а также на резистентность к проводимой противоопухолевой терапии. В обзоре отражены иммунологические характеристики колоректальной карциномы, в том числе в контексте молекулярно-биологических подтипов. Описывается участие клеток иммунной системы (лимфоцитов, макрофагов) и их продуктов (цитокинов, хемокинов) в прогрессировании колоректального рака, в том числе в процессах неоангиогенеза, а также взаимосвязи Т- и В-клеточного состава микроокружения опухоли на течение заболевания. Также в обзоре отображена иммуногеномная стратификация колоректальной карциномы, которая может быть применена для прогнозирования ответа на иммунотерапию колоректального рака.

Ключевые слова: колоректальный рак, молекулярно-генетические подтипы, опухоль-ассоциированные макрофаги, цитокины, хемокины

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Colorectal cancer (CC) occupies a leading position in the structures of morbidity and mortality [1–6]. Despite the successes achieved in recent years in the diagnosis and therapy of cancer (targeted therapy, immunotherapy), the life expectancy of patients with this disease does not increase significantly. The reason for this may be the progression of the disease, as well as the development of resistance to therapy [7–9]. Molecular mechanisms of progression play a key role in metastasis [10].

To date, two classifications of colorectal cancer have been proposed reflecting the molecular genetic characteristics of the tumor [11–13]. In 2012, Cancer Genome presented a molecular analysis of colorectal carcinoma using genome-wide sequencing technology [11]. During the study, CC was divided into 2 groups, the first included tumors with a high mutational load or having microsatellite instability (MSI), the second group consisted of tumors with a low mutational load or having microsatellite stability (MSS).

However, the criteria used in this classification turned out to be insufficient. During the data analysis, new biomarkers of colorectal carcinoma were identified, which formed the basis of the new classification. In 2016, Guinney et al., considering new data from the Consensus Molecular Subtype (CMS) consortium, the CC was divided into 4 subtypes (CMS1-CMS4) (Table. 1) [12]. The first subtype of CMS1 was characterized by the presence of MSI, the phenotype of methylation of CpG islands (CIMP), the presence of a mutation in the BRAF gene and was called MSI – immune. The second subtype of CMS2 is canonical, characterized by the presence of a high level of somatic copies (SCNA), activation of MYC and the WNT signaling pathway. CMS3 or the third subtype is metabolic, it can include tumors with a mixed MSI status, low levels of SCNA and CIMP, and the presence of a mutation in the KRAS gene. The fourth CMS4 is mesenchymal, with the presence of high levels of SCNA, stromal infiltration, activation of TGFß and angiogenesis. At the same time, the authors not only classify colorectal carcinoma into certain subtypes, considering their molecular and genetic characteristics, but also give a prognosis regarding patient survival [12].

For example, patients with CMS1 are less likely to survive a relapse of the disease than patients with other subtypes, and patients with CMS4 have the worst prognosis for overall relapse-free survival compared to other subtypes.

However, this classification is not enough, since the cause of the progression CC is also associated with the molecular heterogeneity of the tumor, which is part of the evolutionary and temporal process [14, 15]. Heterogeneity is also regarded as the cause of resistance to ongoing antitumor therapy (Fig. 1).

Tumor heterogeneity is often caused by a change in the RAS signaling pathway, which, in turn, is a component of the RAS-MEK-ERK cascade. Combinations of drugs, primarily anti-EGFR, are used to overcome resistance to EGFR inhibitors [16]. But even this approach provides only a slight improvement in the

Table 1. Molecular subtypes of colorectal cancer [12]

CMS1 Immune	CMS2 (canonic)	CMS3 (metabolic)	CMS4 (mesenchymal)
14 %	37 %	13 %	23 %
Increased expression of MSI genes; High level of epithelial differentiation; High mutational activity	Epithelial differentiation; High somatic copyability	Mixed status by MSI; Low level of epithelial differentiation; Low somatic copyability	Epithelial-mesenchymal transition; High somatic copyability
BRAF mutations		KRAS mutations	
Immune infiltration	Activation of the WNT and MYC signaling pathway	Metabolic dysregulation	Activation of TGF-b; Stromal infiltration; Angiogenesis

Note: MSI – microsatellite instability; TGF – a transformative growth factor

survival rate of patients with metastatic CC. In order to find alternative ways to overcome resistance to ongoing therapy, as well as markers of drug efficacy, tumor genotyping based on blood samples is carried out, the effect of the immune system on tumor tissue is studied, including the search for new biomarkers.

In the classification proposed by Guinney et al. [12] the immunological characteristics of CC are partially affected, in particular, the CMS1 subtype is characterized by the presence of infiltration of tumor stroma by immune cells. In addition, this subtype carries the ability to have a high level of mutational activity with the formation of neoantigens (resulting from somatic mutation of a tumor cell) that stimulate an antitumor immune response. This explains the high immunogenicity of the tumor and its infiltration by immune cells, especially activated lymphocytes – CD8+ T cells, CD4+ memory T cells, Th1, activated dendritic cells, NK cells and M1 macrophages. It is also known that CMS1 subtype tumors are able to express genes with subsequent release into the intercellular space of CXCL9 and CXCL10 involved in T cell chemotaxis, as well as IL-15, IFNy, CXCL13, etc. [17]. In addition, it has been shown that the expression of molecules of immune control points (PD-1, PD-L1, CTLA-4) of tumors of this subtype allows them to evade immune surveillance [18], although it suggests the effectiveness of immunotherapy with inhibitors of these control points in the treatment of such tumors.

The CMS2 subtype is characterized by low levels of lymphocytes, monocytes and myeloid cells, and, consequently, a weak antitumor response. In addition, tumors of the "canonical" subtype practically do not express PD-1, PD-L1 [12].

Tumors belonging to the CMS3 subtype, as well as tumors with the CMS2 subtype, are characterized by an immunologically depleted cellular composition. However, unlike the previous subgroup, tumor cells carry PD-L1 on their surface, and there are Th17, "naive" B and T cells in their microenvironment [12, 19, 20]. Such a microenvironment, apparently, cannot provide an effective antitumor response, since Th17 has pro-oncogenic properties, and "naive" lymphocytes do not have functional activity.

The fourth subgroup of colorectal carcinomas is characterized by a high level of infiltrating lymphocytes and macrophages, with the M2 phenotype, while the number of M1 is reduced. A high content of regulatory T cells (T-reg) is also found, and the concentration of CD8+, CD4+ T cells is reduced. The presence of TGF-β, CXCL12 and VEGF contributes to the maintenance of the inflammatory environment and, as a result, causes the development and progression of the tumor [12, 13, 19, 20].

A number of authors believe that, knowing the immunological, molecular and genetic component of various subtypes of colorectal cancer, it is possible to predict the response to antitumor treatment [13, 19, 20].

Currently, immunological markers are being ac-

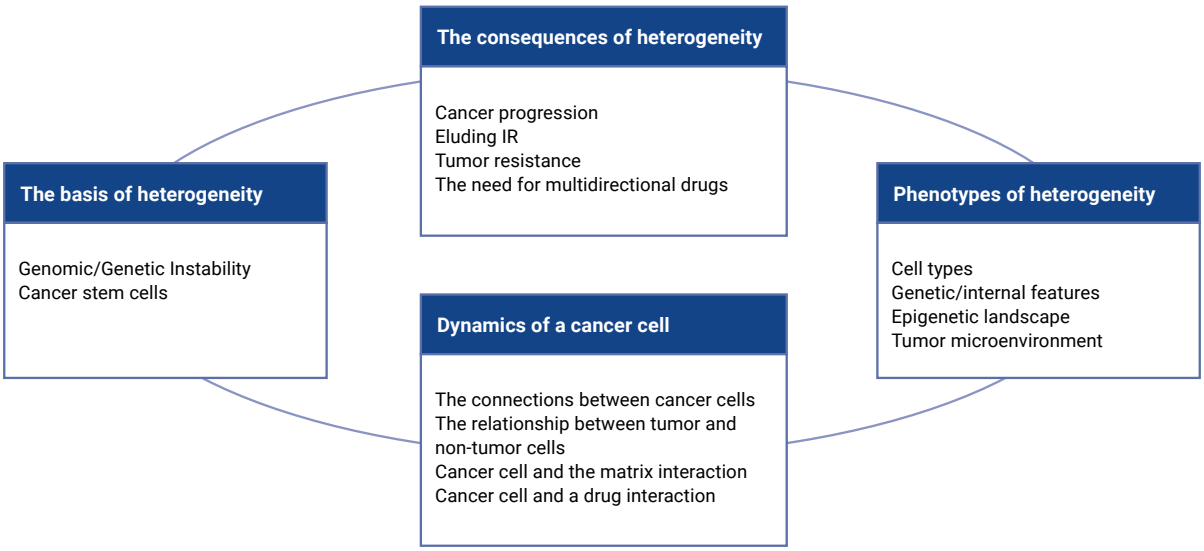

Fig. 1. Principles of evolutionary and temporal heterogeneity of cancer [14]

tively investigated as prognostic indicators of progression [19–21], in particular, not only the type of immune cells infiltrating the tumor, which are part of the tumor microenvironment, but also the density of infiltration by these cells. At the same time, the approach to the study can be complex or multiplex and single-factor – the study of specific biomarkers. The relevance of the study of immunological markers is due to the involvement of immune cells in the progression of cancer [22, 23]. Cytokines and chemokines both form an inflammatory environment and activate antitumor immunity. For example, IL-12, IL-15, IL-18, IFN-γ stimulate the response to tumor antigens, and promote tumor progression – IL-6, IL-17A, IL-22, IL-23; affect neoangiogenesis, growth and survival of tumor cells – TNF-α, EGFR ligands, TGF-β, IL-6 [24]. Tumor-associated macrophages (TAM) play a key role in the development of both an inflammatory response and in the processes of progression and are also a source of a wide range of cytokines.

Macrophages are the most common immune cells in the microenvironment of colorectal carcinoma. Macrophages are able not only to influence the processes of inflammation in the microenvironment, but also participate in carcinogenesis and tumor progression. In addition, they can modulate the response to standard treatment methods (chemotherapy, radiation therapy, therapy with drugs suppressing neoangiogenesis), leading to the development of resistance and subsequent tumor progression [25–28]. For example, the expression of IL-6 and TNF-α macrophages promotes the transmission of signals by tumor cells and the development of resistance to antitumor therapy. The invasion of neoplastic cells is facilitated by the targeted release of cytokines/chemokines, such as EGF, CCCL18, IL-4. Macrophages participate in the processes of neoangiogenesis by stimulating the expression of VEGF-A by endothelial cells, which in turn leads to the formation of an abnormal vascular network, which is characterized by excessive branching, a large number of capillaries, lack of vascular tightness, thereby changing hemodynamics in tumor tissue, making it difficult to deliver drugs. Macrophages are also able to influence cytotoxic lymphocytes by modulating the immune response. The inhibition of the cytotoxic T lymphocyte response can occur through the expression of B7 family ligands or by the release of IL-10 through CCL22 with suppression of IL-12 production by dendritic cells.

The immunosuppressive role is played by regulatory T cells (T-reg) due to the production of anti-inflammatory cytokines IL-10 and TGF-β [29]. B-cell infiltration in CC is often observed due to the large representation of these cells in tertiary lymphoid structures that originate from peripheral lymphoid tissue under prolonged exposure to inflammatory

GROUP A		GROUP B		GROUP C		GROUP D	
14 %		26 %		16 %		43 %	
MSI-H	(82 %)	MSS	(86 %)	MSS	(94 %)	MSS	(75 %),
Right side	(82 %)	Left side	(63 %)	Left side	(94 %)	MSI	(25 %)
CIMP high	(68 %)	CIMP negative	(77 %)	CIMP negative	(66 %)	Left side	
BRAF mt	(50 %)	BRAF mt	(4 %)	BRAF mt	(3 %)	CIMP negative	(69 %)
KRAS mt	(18 %)	KRAS mt	(47 %)	KRAS mt	(22 %)	KRAS mt	(49 %),
PI3K mt	(39 %)	TP53 mt	(65 %)	TP53 mt	(62 %)	NRAS mt	(13 %)

Fig. 2. Cluster typing of the immune response (CIRC)

Table 2. Genes of clusters coordinating the immune response [33]

Group	Genes						
Group A	HLA-DQA1	HLA-DQA2	HLA-DRB5	HLA-DMA	PDCD1LG2	ICAM1	CD274
Group B	STAT1	IRF1	IFNG	CTLA4	TBX21	CCL5	LAG-3
Group C	CD247	ICOS	IL18RAP	GNLY	CXCL10	HLA-DPB1	HLA-DPA1
Group D	HLA-DMB	HLA-DRA	HLA-DMA	CD80	HLA-DOA	CD4	HAVCR2

signals mediated by chemokines and cytokines [30]. B cells in the tumor microenvironment along with the T-cell component (cytotoxic CD3+CD4+ and CD3+CD8+ T cells, other subpopulations of T cells) are associated with a favorable prognosis. However, the presence of macrophages in the CC microenvironment stimulates the development of inflammation and, as a result, affects tumor progression [31].

The phenomena occurring in immunocompetent cells of the CC microenvironment may also differ at the molecular genetic level. Thus, Laghi L., et al., in 2020 published a paper aimed at identifying the relationship between the genetic and immune components of colorectal cancer [32]. It is known that tumors with MSI have a large number of tumor infiltrating lymphocytes (TILs), however, tumors with MSS may also have high levels of TILs. A favorable prognosis in CC is associated with a high level of TILs, which in turn can be a biomarker for identifying a cohort of patients with a low probability of disease recurrence and influence the choice of therapy.

The search for biomarkers capable of predicting the effectiveness of therapy in CC continues. Lal N, et al., published a paper on the immunogenomic stratification of colorectal carcinoma used to describe the response to CC immunotherapy [33]. The basis for stratification was cluster typing of the immune response (CIRC) (Fig. 2) [33], which divides patients with CC into four groups depending on the level of expression of a set of genes that do not completely coincide with the molecular genetic subtypes (Table 2).

Stratification links the genetics and immunobiology of CC. At the same time, the expression of immune control points and cytokine/chemokine genes were found to correspond to the expression of some variants of the main histocompatibility complex HLA (Table 2).

Group A is characterized by MSI-H and POLE gene mutations, high mutational load and high immune infiltration, which can be useful when using immune checkpoint inhibitors (ICIs). Whereas in group D and B, mutations in the RAS family genes were present, and these patients were resistant to ICI therapy. Nevertheless, the question remains which of the CC classifications to focus on when predicting the response to, particularly, immunotherapy treatment [34]. The development of new approaches to the stratification of patients with CC continues, as well as the search for new directions to eliminate resistance in the population of patients resistant to existing treatment methods.

CONCLUSION

The tumor microenvironment by immune cells plays one of the key roles in the progression of colorectal cancer and the mechanisms of development of resistance to therapy, which may be significant for a personalized approach to antitumor treatment and the search for predictive markers of the effectiveness of therapy, including immunological ones.

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REVIEW

Mitochondrial transplantation: new challenges for cancer

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ABSTRACT

This review discusses the uniqueness of mitochondria providing normal cellular functions and at the same time involved in many pathological conditions, and also analyzes the scientific literature to clarify the effectiveness of mitochondrial transplantation in cancer treatment. Being important and semi-autonomous organelles in cells, they are able to adapt their functions to the needs of the corresponding organ. The ability of mitochondria to reprogram is important for all cell types that can switch between resting and proliferation. At the same time, tumor mitochondria undergo adaptive changes to accelerate the reproduction of tumor cells in an acidic and hypoxic microenvironment. According to emerging data, mitochondria can go beyond the boundaries of cells and move between the cells of the body. Intercellular transfer of mitochondria occurs naturally in humans as a normal mechanism for repairing damaged cells. The revealed physiological mitochondrial transfer has become the basis for a modern form of mitochondrial transplantation, including autologous (isogenic), allogeneic, and even xenogenic transplantation. Currently, exogenous healthy mitochondria are used in treatment of several carcinomas, including breast cancer, pancreatic cancer, and glioma. Investigation of the functional activity of healthy mitochondria demonstrated and confirmed the fact that female mitochondria are more efficient in suppressing tumor cell proliferation than male mitochondria. However, tissue-specific sex differences in mitochondrial morphology and oxidative capacity were described, and few studies showed functional sex differences in mitochondria during therapy. The reviewed studies report that mitochondrial transplantation can be specifically targeted to a tumor, providing evidence for changes in tumor function after mitochondrial administration. Thus, the appearance of the most interesting data on the unique functions of mitochondria indicates the obvious need for mitochondrial transplantation.

Keywords: mitochondria, mitochondrial therapy, mitochondrial transfer, malignant tumors

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3.1.6. Онкология, лучевая терапия
ОБЗОР

Митохондриальная трансплантация – новые вызовы раку

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РЕЗЮМЕ

В представленном обзоре обсуждаются вопросы, касающиеся уникальности митохондрий, обеспечивающих нормальные клеточные функции, в то же время их участие во многих патологических состояниях организма, а также анализируется существующая литература с целью разъяснения эффективности трансплантации митохондрий при лечении злокачественных заболеваний. Являясь важными и полуавтономными органеллами в клетках, они способны адаптировать свои функции к потребностям соответствующего органа. Возможность митохондрий перепрограммироваться важна для всех типов клеток, которые могут переключаться между состоянием покоя и пролиферацией. Вместе с тем митохондрии опухолей претерпевают адаптивные изменения для ускорения размножения опухолевых клеток в кислой и гипоксической микросреде. Согласно появляющимся данным стало известно, что митохондрии могут выходить за границы клеток, перемещаться между клетками организма. Межклеточный перенос митохондрий естественным образом происходит у людей как нормальный механизм восстановления поврежденных клеток. Выявленный физиологический митохондриальный перенос стал основой для создания современной формы трансплантации митохондрий, включая аутологичную (изогенную), аллогенную и даже ксеногенную трансплантацию. В настоящее время экзогенные здоровые митохондрии используются для лечения некоторых карцином, включая рак молочной железы, рак поджелудочной железы и глиому. Исследование функциональной активности здоровых митохондрий привело к обнаружению и доказательству того, что женские митохондрии обладают более высокой эффективностью подавления пролиферации опухолевых клеток, чем мужские митохондрии. Вместе с тем были описаны тканеспецифические половые различия в морфологии митохондрий и окислительной способности, и лишь немногие исследования показали функциональные половые различия митохондрий при терапии. Рассмотренные в обзоре исследования показывают, что трансплантация митохондрий может быть специфически нацелена на опухоль, с предоставлением доказательств изменений в функции опухоли после введения митохондрий. Таким образом, появление интереснейших данных об уникальных функциях митохондрий свидетельствуют об очевидной необходимости митохондриальной трансплантации.

Ключевые слова: митохондрии, митохондриальная терапия, митохондриальный перенос, злокачественные новообразования

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INTRODUCTION

Mitochondria have played a fundamental role in the evolution of complex organisms. Being important and semi-autonomous organelles in cells, they are able to adapt their functions to the needs of the corresponding organ. Mitochondria can reprogram their intended purpose for the desired result: for an exceptional supply of energy to maintain the functioning of heart muscle cells throughout life or to control metabolic processes in secreting organs, for example, to support the work of hepatocytes and the liver. The ability of mitochondria to reprogram is important for all cell types that can switch between resting and proliferation, such as stem cells and immune cells. Most chronic diseases are characterized by a violation of mitochondrial regulation, which has been revealed in cardiovascular diseases, metabolic syndrome, neurodegenerative diseases, immune system disorders and malignant neoplasms [1–7].

The purpose of this review article was to evaluate new possibilities in the treatment of malignant neoplasms during mitochondrial transplantation.

Functional and dysfunctional multiplicity of mitochondria

Malignant tumors invariably rearrange their metabolism, promoting cellular plasticity with adaptation to the constantly changing availability of nutrients and the acquisition of aggressive disease traits, including the ability to metastasize. Cancer metabolism has long been equated with the predominant use of glycolysis by tumor cells even in the presence of oxygen, the so-called Warburg effect [8]. However, it is now known that the functions of mitochondria in tumor metabolism are broader, e. g. the use of oxidative bioenergetics, a change in the redox balance, the inclusion of multiple mechanisms of cell survival and retrograde expression of nuclear genes, as well as the effect on the primary and metastatic spread of a malignant tumor [9–11]. Interestingly, just like differentiated cells, mitochondria perform specialized functions unique to specific organs and tissues. For example, mitochondria in the liver are mainly involved in biosynthetic processes, and mitochondria in the heart or muscles mainly produce ATP. Mitochondria in adipocytes play a crucial role in regulating adipocyte differentiation, insulin sensitivity, and adaptive thermogenesis [12]. Analysis of the mitochondrial proteome isolated from various tissues such as the brain, liver, heart and kidneys of rats showed mitochondrial heterogeneity specializing in different functions between tissues. Abnormalities in mitochondria disrupt basic physiological functions such as ATP production, oxidative phosphorylation, reactive oxygen species (ROS) production and Ca^{2+} regulation, all of which are considered mitochondrial dysfunction. In addition, these unique organelles, which are important for normal cellular function, can be involved in many pathological conditions. Mitochondria are present in every cell of the human body, with the exception of red blood cells – erythrocytes. The production of ATP by mitochondria leads to the formation of small amounts of potentially destructive free radicals known as reactive oxygen species (ROS). These radicals are secondary messengers in vital cellular signaling cascades for normal biological processes. However, the accumulation of byproducts of ATP production can harm the cell and provoke damage to cellular organelles, as well as disruption of metabolic processes [13].

It is obvious that mitochondria are the most important organelles responsible for cell survival and apoptosis. Healthy mitochondria are essential for maintaining the normal functioning of cells. At the same time, accumulated research data indicates that tumor mitochondria undergo adaptive changes to accelerate the proliferation of tumor cells in an acidic and hypoxic microenvironment [14]. There is increasing evidence that mitochondrial metabolism and function are indispensable in oncogenesis and cancer progression, which makes mitochondria and their functions likely targets for antitumor therapy [15].

Although the mechanisms of mitochondrial reprogramming in cancer have recently received more attention, the role of organelle in this process has not been widely considered [16, 17]. In fact, the microenvironment in which the tumor grows is extremely unfavorable for mitochondria, since unstable oxygen concentrations and oxidative radicals can disrupt the integrity of organelles, disintegrate the regulation of many mitochondrial functions and activate cellular death [18]. Therefore, the way how mitochondria cope with the loss of their "functional form" remains unclear, and the effect of substandard or damaged mitochondria on tumor signs has not been studied [19]

Mitochondrial movement as a basis for mitochondrial therapy

Endosymbiotic theory suggests that mitochondria were once primary free-living unicellular organisms that may have been absorbed by larger, probably anaerobic cellular organisms in order to use them for more efficient aerobic energy production [20]. This "adoption" and billions of years of evolution have led to the complexity of eukaryotes. The proof of this theory is that mitochondria contain their own DNA (mtDNA) in the form of ring DNA, similar to that found in bacteria, and also contains two lipid bilayers. Mitochondria, like bacteria, are equipped with an intracellular mechanism necessary to produce 13 of their own mitochondrial proteins, but at the same time use nuclear DNA to produce other key proteins. It is due to this endosymbiotic origin that the internalization of mitochondria by recipient cells is possible [21].

Emerging data show that mitochondria can transcend cell boundaries, move between mammalian cells, radically challenging the concepts of intracellular segregation of mitochondria and inheritance of mitochondrial DNA, i. e. the mtDNA. Their signaling role may extend to intercellular communication, showing that the mitochondrial genome and even entire mitochondria are indeed mobile and can mediate information transfer between cells. This newly discovered process of mobile transfer of mitochondria and mtDNA has been called the "momiome" to denote all "mobile functions of mitochondria and the mitochondrial genome" [22]. Mitochondrial intercellular transfer promotes the integration of mitochondria into the endogenous mitochondrial network of recipient cells, contributing to changes in their bioenergetic status and other functional properties of recipient cells not only *in vitro*, but also *in vivo*. Moreover, transcellular transfer of mitochondrial genes can have serious consequences in the pathophysiology of mitochondrial dysfunction [23].

It has been reported that intercellular mitochondrial transfer naturally occurs in humans as a normal mechanism for repairing damaged cells [24, 25]. This physiological phenomenon inspired researchers to create a modern form of mitochondrial transplantation, including autologous (isogenic), allogeneic and even xenogenic transplantation [4, 26, 27]. Given that mitochondrial dysfunction may be at the center of devastating pathological conditions, mitochondrial transfer, called mitochondrial transplantation, has high therapeutic potential in modern medicine.

Mitochondrial transplantation is an innovative strategy for the treatment of mitochondrial dysfunction, which allows overcoming the limitations of agent–based therapy. Mitochondrial replacement, transplantation, or transfer is a new intervention and treatment for patients diagnosed with mitochondrial disease [28]. Mitochondrial transfer is based on the concept of targeted tRNA therapy. Treatment strategies for mitochondrial dysfunction are usually divided into the following categories: enhancing mitochondrial biogenesis; reducing dysfunctional mitochondria and replacing them with active ones; delivery or replacement of dysfunctional components; intervention in the consequences of mitochondrial dysfunction and reprogramming of the mitochondrial genome [29, 30]. It is believed that mitochondria persist in cells throughout their lives. The prerequisite for mitochondrial transfer is that the cell can perceive many different environmental signals and subsequently absorb, transfer, process and integrate foreign material. Which signals trigger mitochondrial transfer is of great importance for further theory and treatment. Current data have proven that mitochondrial transfer between cells is often triggered by multiple intracellular and extracellular events of the recipient cell. These events can act as "find me" or "save me" signals, recruiting the appropriate donor mitochondria to provide them to recipient cells [13].

Several *in vitro* studies have shown that intercellular mitochondrial transfer occurs naturally. When DsRed-labeled mitochondria isolated from mesenchymal cells (EMC) originating from the endometrial glands of the human uterus were co-incubated with isogenic EMC for 24 hours, the accumulation of exogenous mitochondria in the cytoplasm of recipients was observed using imaging of living fluorescent cells [31]. In another study, it was also observed that xenogenic transfer of mitochondria isolated from mouse liver tissue to human cells devoid of functional mitochondria (cells p 0) restores respiratory function [32]. These results prove the possibility of treating mitochondrial diseases with mitochondrial transplantation.

In addition to the observed transfer of mitochondria in *in vitro* experiments, the possibility of introducing mitochondria directly into living organisms seems relevant. The mitochondria used for injection can be autologous, allogeneic, or even xenogenic. Doulamis I. P. et al. injected allogeneic or autologous mitochondria of muscle cells into damaged areas of the heart of rats with diabetes, both variants of mitochondria led to the restoration of left ventricular function and a decrease in the size of infarction [33]. Mitochondria can be injected directly into the damaged area or elsewhere. For example, Lin H. S. et al. mitochondria were injected into the spleen for the treatment of ischemically damaged liver [34]. In addition, in the past, researchers more often injected mitochondria directly into the regional ischemic zone to repair myocardial damage, and recently decided to inject mitochondria into the left coronary mouth or coronary artery [33, 35]. Local intracerebral or systemic intraarterial injection of mitochondria can significantly restore the area of cerebral infarction and the death of neuronal cells [36]. In addition, intraarterial injection or intravascular delivery of mitochondria into blood vessels has been performed to treat acute kidney injury or lung injury [37]. A recent study has shown the existence of intact and functional mitochondria in human peripheral blood [26]. Moreover, there is much evidence that there are many mitochondrial components in the blood, such as cell-free circulating mtDNA, vesicles of mitochondrial origin and peptides of mitochondrial origin, and these components increase in disease [38–40]. Although the significance of their presence in the blood and their association with disease are unclear, the presence of these components demonstrates that mitochondria can play a signal-regulating role through circulation in distant cells, even if they are fragmented. Accordingly, intravascular administration of mitochondria can be promising if we understand in advance the existence of mitochondria in the blood, the biological role of mitochondrial components.

Dysfunctional dominance of malignant mitochondria and the possibility of counteraction

The mitochondria of malignant cells play a key role in the interaction of tumor cells with the tumor microenvironment [41]. As recent scientific studies have shown, tumors are not only composed of malignant cells, they are a complex system of tumor and non-tumor cells that create symbiotic relationships in the tumor microenvironment, contributing to survival and resistance to chemotherapy. Malignant cells are able to displace entire mitochondria or some of their components, including mtDNA, cytochrome C, and formylated peptides into the tumor microenvironment [42]. They, in turn, function as damage-associated molecular patterns (DAMPs) that are released from damaged or "dying" cells and activate the innate immune system.

Elliott R. L. et al. (2012) found that mitochondria purified from immortalized, untransformed MCF-12A breast epithelial cells can successfully penetrate human breast cancer cell lines and suppress them depending on the dose. Mitochondria from MCF-12A cells can also be transferred to human breast cancer MCF-7 cell lines, which is accompanied by increased sensitivity to chemotherapy with doxorubicin, abraxane or carboplatin [43]. This is the first publication concerning the transfer of mitochondria that promote apoptosis of malignant cells and increase sensitivity to drugs.

Accumulating research data show that tumor mitochondria undergo adaptive changes to accelerate the rapid proliferation of tumor cells in an acidic and hypoxic microenvironment [14]. Thus, it is assumed that the introduction of healthy mitochondria into tumor cells is highly effective in preventing tumor growth [44]. Currently, exogenous healthy mitochondria are used to treat several carcinomas, including breast cancer, pancreatic cancer and glioma, and excellent antitumor efficacy of healthy mitochondria has been shown [45–47]. At the same time, the authors, based on the obtained biochemical data, noted the fact that healthy mitochondria after mitochondrial transplantation can significantly reduce the ability to oxidative phosphorylation (OXPHOS) and induce apoptosis in tumor cells. However, the molecular signaling mechanism of this process remains unclear.

The mechanism of mitochondrial penetration, immune reactions

Intercellular mitochondrial transfer occurs through tunneling nanotubes (TNT), extracellular vesicles (EV) and cell fusion. Recently, functionally active mitochondria free of cells and cytoplas-

mic membrane have been observed in blood and conditioned medium for cell culture [48]. Although the role of extracellular mitochondria in intercellular communication has yet to be fully understood, practical approaches aimed at transferring intact mitochondria to target cells have been developed previously.

The mechanism of mitochondrial penetration into cells may be related to macropinocytosis-mediated endocytosis, since a macropinocytosis inhibitor can prevent the internalization of mitochondria by cells. Moreover, mitochondria are considered as systemic intermediaries in intercellular communication [49]. It is also known that mitochondria can be absorbed by various cell types, as has been shown in *in vitro* and *in vivo* studies [50]. In addition, mitochondria in the blood can activate the immune system by increasing the activity of phagocytes and T cells, which can to a certain extent enhance the antitumor effect of mitochondria [51].

To date, some studies have discussed the immune reactions that occur during mitochondrial transplantation – MT. Understanding their involvement in the effectiveness of MT would be valuable to reduce possible risks. With existing mitochondrial disease, transplantation of mitochondria obtained from autologous cells is possible without inflammation and autoimmune reactions [52]. Some researchers believe that autologous mitochondrial transplantation may have more effective results. However, in some cases, including diseases associated with mitochondria, or in some of the most severe patients, isolation of their own mitochondria is impossible. On the other hand, some patients require multiple series of injections. Therefore, in this regard, transplantation of heterologous mitochondria is inevitable [53]. The main possible problems of heterogeneous mitochondrial transplantation are immune system reactions and damage-related molecular pattern (DAMP). It should be noted that in all previous studies, only one injection of mitochondria was reported. And what happens after a series of injections of mitochondria into damaged tissues? McCully J. D. et al. (2017) conducted a study to find out the behavior of the immune system after direct or indirect autogenic and allogeneic injections, single and serial injections, as well as various numbers of isolated mitochondria (1×105, 1×106 or 1×107 mitochondria). The data obtained showed that the level of immune system profiles, including IL-1, IL-4, IL-6, IL-12, IL-18, IP-10, macrophage inflammatory protein MIP-1 α and MIP-1 β did not change. Single or serial injections of mitochondria did not show the presence of DAMP in the recipient's tissues [54]. Ramirez-Barbieri G. et al. (2019) investigated the immune response and damage-related molecular patterns (DAMPs) In mice, after single or multiple intraperitoneal injections of allogeneic mitochondria, it was found that serum cytokine and mtDNA levels did not increase either after autologous or after allogeneic mitochondrial injection [55].

Sex-related features of mitochondria

Mitochondria are an almost exclusive legacy of the mother in evolution, and during transplantation therapy, sex differences in the functioning of mitochondria may occur. It was previously reported that the mitochondria of female animals (female mitochondria) are more sensitive to stress and better adapted to combat adverse conditions, therefore, it was assumed that female mitochondria have different activity in antitumor growth compared with the mitochondria of males [56].

A number of reports have described tissue-specific sex differences in mitochondrial morphology and oxidative capacity, while only a few studies have shown functional differences in mitochondria during therapy. At the same time, it has been shown that the mitochondria of women have a higher protein content and the ability to produce ATP than in men [57]. According to the available limited data, female mitochondria have more favorable mitochondrial-nuclear communication in response to stress compared to male mitochondria [58].

Yu Z. et al. (2021) evaluated the activity of mitochondria isolated from female and male mice, and the results showed that female mitochondria showed higher activity and ability to produce ATP than male mitochondria. Subsequently, antitumor mitochondrial effects in a number of experiments, both *in vitro* and *in vivo* models, proved that female mitochondria have a higher efficiency of suppressing tumor cell proliferation than male mitochondria. The study also showed that female mitochondria can induce a more sustained stress response to gene transcription than male mitochondria in tumor cells, suggesting that female mitochondria are more sensitive to the hypoxic microenvironment of the tu-

mor than male mitochondria, and ultimately lead to a stronger antitumor effect. The authors used intact mitochondria to study their antitumor activity when administered intravenously. This study demonstrated a new understanding of mitochondrial function in the development of melanoma and suggests that healthy mitochondria inhibit tumor cell proliferation by preventing transcription of tumor genes. General downregulation of genes leads to cell cycle arrest and stagnation of cell proliferation, as well as activation of autophagy and apoptosis, which ultimately leads to an obvious inhibition of melanoma growth after mitochondrial transplantation therapy [59].

CONCLUSION

Today, mitochondria are much more than just the "powerhouse" of the cells. Mitochondrial transplantation therapy has been an active area of research for the treatment of diseases related to mitochondrial dysfunction, from animal studies to clinical trials. However, the specific mechanism providing antitumor activity of healthy mitochondria has yet to be defined. The mechanism of intercellular mitochondrial transfer is still partially understood and requires further research, while its targeting may provide new opportunities in the treatment of malignant neoplasms. Evidence that mitochondrial transfer can occur in a similar way in solid and hematological tumor cells further increases the importance of this process as a basis for mitochondrial transplantation. In addition, the involvement of mitochondrial transfer in cancer progression and the development of chemoresistance may explain the still unclear mechanisms of action of some anticancer drugs. It has been proven that the therapeutic effect of mitochondrial transplantation is a potential method of treating diseases associated with mitochondria. However, there are several problems that need to be solved so that the treatment of the disease with mitochondrial transplantation can be effectively applied to humans.

Most studies emphasize that the isolation of mitochondria should be completed in a short time at a low temperature, since they are very sensitive, and their activity and survival are rapidly decreasing. In addition, there is currently no method for long-term storage of mitochondria, so they should be used immediately after isolation. Therefore, a protocol for the optimal method of mitochondrial isolation and storage, which maintains the integrity of mitochondria and ensures longer survival, should be developed to enable clinical use.

Since mitochondria are easily obtained from cultured cells, and the technology of mitochondrial isolation and preservation is becoming more mature, it is expected that large-scale mitochondrial donation centers will be established in the future. Thus, when autologous transplantation cannot be performed, it is possible to find a compatible mitochondrial donor just in time.

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